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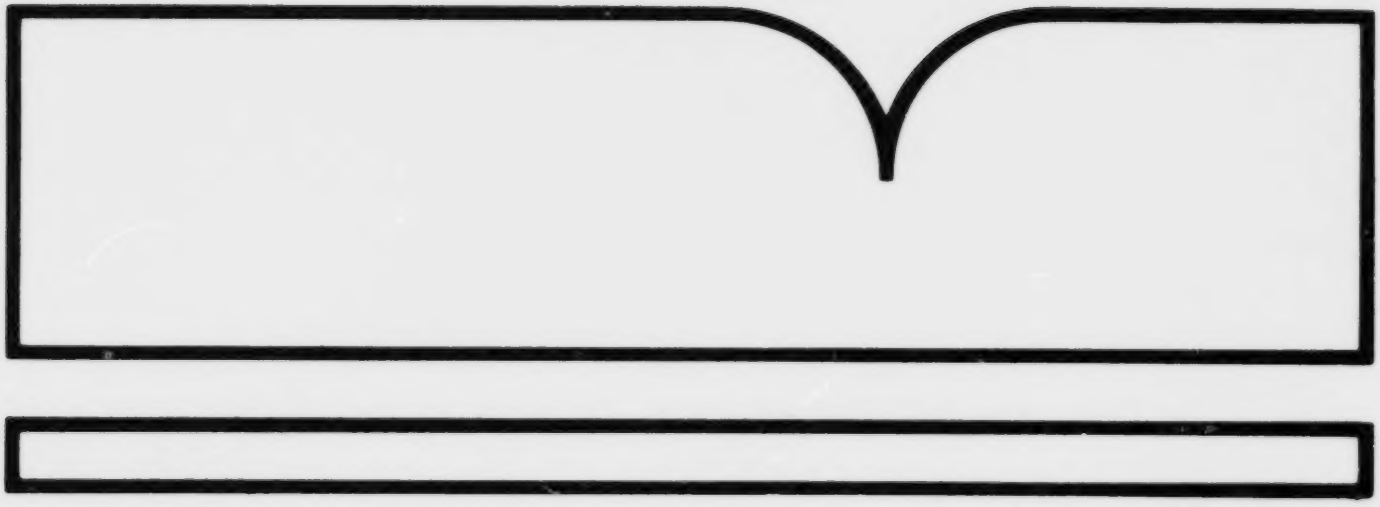
DRINKING WATER CRITERIA DOCUMENT

Dynamac Corporation
Rockville, MD

May 90



U.S. Department of Commerce
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DRINKING WATER CRITERIA DOCUMENT

FOR

ATRAZINE

Updated and revised by

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Prepared for

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Office of Drinking Water
U.S. Environmental Protection Agency
Washington, DC 20460

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FOREWORD

Section 1412 (b)(3)(A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the Environmental Protection Agency to publish Maximum Contaminant Level Goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and which is known or anticipated to occur in public water systems. The MCLG is nonenforceable and is set at a level at which no known or anticipated adverse health effects in humans occur and which allows for an adequate margin of safety. Factors considered in setting the MCLG include health effects data and sources of exposure other than drinking water.

This document provides the health effects basis to be considered in establishing the MCLG. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology, and mechanisms of toxicity were evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document was comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature data base in support of this document includes information published up to August 1988; however, more recent data may have been added during the review process.

When adequate health effects data exist, Health Advisory values for less-than-life-time exposures (One-day, Ten-day, and Longer-term, approximately 10% of an individual's lifetime) are included in this document. These values are not used in setting the MCLG, but serve as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

Michael B. Cook
Director
Office of Drinking Water

I. SUMMARY

Atrazine, 2-chloro-4-ethylamino-6-isopropylamino-s-triazine, has moderate solubility in water (70 mg/L) and is readily soluble in most organic solvents. Atrazine is widely used as a selective herbicide for the control of weeds in corn, sorghum, rangeland, sugarcane, macadamia orchards, pineapples, and turf grass sod.

Although relatively stable in solid form or in neutral solutions, atrazine is subject to breakdown in soil by microbial action and photodecomposition to form dealkylated metabolites, hydroxyatrazine, and nonextractable (bound) residues. Under typical conditions, residual phytotoxicity persists for 3 to 12 months. Half-lives of atrazine in soil range from 20 to 101 days. Atrazine has low potential for bioaccumulation.

The toxicokinetics of atrazine have not been extensively studied. In one study, in which rats were given 0.53 mg atrazine by stomach tube, absorption was about 80%. Absorbed atrazine was found to be distributed throughout the body, with levels in kidney, liver, and lung tissue being higher than levels in fat and muscle. Excretion of the ingested atrazine was primarily in the urine (65.5%), with 20.3% excreted in the feces. The remainder (15.8%) was still present in tissues after 72 hours. Results of one oral-dosing study in rats indicated that urine was the preferred route of excretion, representing 74% of the dose regardless of sex, dose, or pretreatment regimen. Fecal excretion was 19%. A whole-body half-life of elimination was 31.3±2.8 hours. Subchronic dosing of atrazine revealed highest tissue levels in red blood cells but no alteration in the pattern or the first-order kinetics of atrazine observed in animals given a single oral dose.

Dechlorination of the triazine ring and N-dealkylation appeared to be the primary metabolic pathway in the rat, with both the mono- and di-dealkylated metabolites being identified. Oxidation of the alkyl substituents appeared to be a minor and secondary metabolic route. No evidence of ring cleavage was observed. In some species, hydrolysis of the 2-chloro group may also occur. Conjugation of atrazine and its metabolites with glutathione by liver cytosol has been demonstrated *in vitro*, but its significance *in vivo* has not been determined. In addition to the available acceptable studies, there is a need for more research to identify fecal metabolites in male and female rats as well as to address the discrepancies observed in the percent elimination of atrazine and atrazine metabolites in urine and feces.

The principal routes of atrazine exposure in humans are drinking water, food, and air. Reported concentrations of atrazine in drinking water range from 0 to 15.9 ug/L, with a median level below 0.1 ug/L. Although tolerances have been established for atrazine in or on raw agricultural products, there are insufficient data on which to base an estimate of the intake of atrazine from food or ambient air. Therefore, insufficient data exist to determine which of the three sources is the major contributor to total intake. Atrazine has a low to moderate acute oral and dermal toxicity. It is a moderate eye irritant and a slight skin irritant but not a sensitizer of skin.

Acute oral LD_{50} values for atrazine in hamsters and rats range from 672 to 3,000 mg/kg. Toxic signs reported to accompany acute exposure include ataxia, diarrhea, oral discharge, and chromorhinorrhea, with histological changes in the lung, heart, liver, spleen, kidney, and brain. The acute oral LD_{50} in mice was reported to be >3,000 mg/kg. A single oral dose of 100 mg/kg was reported to cause hypotension in cats and antidiuresis in dogs.

In short-term studies, no effect was observed in mice fed doses of atrazine up to 150 mg/kg/day for 28 days. Dietary levels of 450 mg/kg/day resulted in 20% mortality but no evidence of gross pathology, and doses of 1,500 or 4,500 mg/kg/day caused weight loss, muscle weakness, tremors, and increased mortality. Rats receiving doses of atrazine of 100 to 600 mg/kg/day for 14 days showed dose-related increases in electrolyte and protein excretion, indicating a significant effect on kidney function. An effect of atrazine on rat nerve tissue was also noted, with a decrease in the axonal area of sciatic nerve fibers. However, no behavioral effects were noted in rats, during feeding of atrazine at levels of 37.5 and 75 mg/kg/day over a 6-week period.

In one study in sheep, doses of 5 mg/kg/day for 10 days produced ataxia, anorexia, and histopathologic signs in the kidney, liver, and lung. In another study in sheep, doses up to 25 mg/kg/day for 5 weeks produced no visible effects, while doses of 50 mg/kg/day caused weight loss, and doses of 100 to 400 mg/kg/day caused lethality. Cattle and sheep fed hay from a field sprayed with atrazine (average daily atrazine intake of about 20 to 40 mg/kg/day) showed no significant change in weight gain, clinical chemistry, or histologic appearance of tissues.

Adequate long-term feeding studies in rats and dogs were available for atrazine.

Dogs fed 0.35 mg/kg/day for 2 years showed no adverse effects, while dogs fed 3.5 mg/kg/day had decreased food intake, and dogs fed 35 mg/kg/day showed decreased food intake, weight loss, increased adrenal weight, decreased hematocrit, and occasional tremors or stiffness in rear limbs. In a 1-year feeding study in dogs, a dose of 5 mg atrazine/kg/day decreased P-II waves in

females and moderate atrial dilation was seen in males dosed 5 and 34 mg/kg/day. At 34 to 414 mg/kg/day, significant electrocardiogram (EKG) alterations and severe cardiac lesions were observed. A dose of 5 mg/kg/day was determined to be the NOAEL and a dose of 34 mg/kg/day was determined to be the LOAEL.

In a recent two-year feeding study at doses that ranged from 0.5 to 50 mg/kg/day (10 to 1,000 ppm) in Sprague-Dawley rats, increased female mortality was noted at the high dose, a NOAEL was noted at 3.5 mg/kg/day for decrease in body weight gain in both sexes. However, a dose-related increase in mammary gland tumors was noted at this dose level and above. No effects were noted at 0.5 mg/kg/day in this study.

In a three-generation feeding study with rats, doses of 2.5 or 5 mg/kg/day had no measurable effect on reproductive success and showed no developmental effects.

In a two-generation feeding study in rats, exposure to 500 ppm atrazine (25 mg/kg/day) for 10 weeks before mating caused a significant ($p < 0.05$) decrease in [illegible] weight and body weight gains; however, food consumption was also depressed. In pups of both generations, a significant ($p < 0.05$) reduction in body weight was noted; this effect was dose-related in the second generation at both the 50- and 500-ppm (2.5 and 25 mg/kg/day, respectively) levels on postnatal day 21. No histopathological effects were noted in either parental generation, and no signs or symptoms of toxicity were observed at the low-dose (10 ppm; 0.5 mg/kg/day). This study identified in rats a maternal toxicity NOAEL of 2.5 mg/kg/day; and a LOAEL of 25 mg/kg/day. The reproductive NOAEL was 0.5 mg/kg/day and LOAEL was 2.5 mg/kg/day based on reduced pup weight.

In a rat teratology study, doses of 10 mg/kg/day had no measurable feto-toxicity when given orally to pregnant rats on days 6 to 15 of gestation; however, doses of 70 or 7,000 mg/kg/day produced retarded skeletal development along with maternal toxicity. Doses up to 40 mg/kg/day fed to rats throughout gestation produced no effects on litter size or weight.

Rabbits receiving atrazine on days 7 through 19 of gestation showed no effects at 1 mg/kg/day; however, maternal toxicity was noted at 5 and 75 mg/kg, but developmental toxicity was shown only at 75 mg/kg/day. Therefore, atrazine appears to be embryotoxic only at relatively high concentrations.

In pregnant mice, subcutaneous injections of atrazine at 46 mg/kg/day on gestational days 6 through 15 did not produce a significant increase in fetal anomalies. In pregnant rats, subcutaneous injections of atrazine at doses up to 200 mg/kg/day on gestational days 3, 6, and 9 had no effect on litter size, but doses of 800 or 2,000 mg/kg/day produced embryolethality.

A large body of information on the mutagenic properties of atrazine exists in the literature. There is general agreement that atrazine is not mutagenic in bacteria in the presence of mammalian microsomes. Gene mutation in lower eukaryotes seems to be achieved only by plant-activated conversion of atrazine to a reactive form. The relevance of this finding to human health is unclear; however, further characterization of the role of plant metabolism toward a possible mammalian genotoxic hazard requires further examination. No definitive conclusions can be drawn from *in vivo* somatic and germinal cell studies until atrazine is adequately tested in well-controlled and well-conducted *in vivo* cytogenic studies. Similarly, studies evaluating other modes of genotoxic action provide little meaningful data.

The ICPEMC (International Commission for Protection Against Environmental Mutagens and Carcinogens) weight-of-evidence scheme was applied to the available atrazine genetic toxicology data, and it was indicated that atrazine should be considered nonmutagenic. However, it was concluded that the use of the weight of evidence approach at the present time is not recommended until additional in vivo data are available in order to adequately assess this endpoint of toxicity for atrazine.

Evidence for the carcinogenicity of atrazine is equivocal. No evidence of increased tumor frequency was observed in male and female mice fed up to 386 and 483 mg atrazine/kg/day, respectively, for 18 months. In two other lifetime rodent studies of questionable validity, mice fed up to 150 mg/kg/day and rats fed up to 5 mg/kg/day showed no excess tumor development over control animals. In contrast, in a recent study in Sprague-Dawley, rats fed 0.5 to 50 mg atrazine/kg/day female rats receiving atrazine at 3.5 mg/kg and higher had a statistically significant increase in mammary gland fibroadenomas, adenocarcinomas, and total mammary gland tumors compared to control rats; there were also indication of reduced latency of the adenocarcinomas at the one-year interim sacrifice; in addition, structure-activity relationship with three other symmetrical triazines, propazine, simazine and terbutryn, indicated the increased incidence of mammary gland tumors in the same strain of rat. Therefore, atrazine is classified in oncogenicity Group C: possible human carcinogen.

There is little information regarding the health effects of atrazine in humans. One study reported contact dermatitis in a farmer who had prior sensitivity to propachlor. One epidemiologic study reproted some correlation between atrazine useage and 1- and 30-minute bilirubin values in a small number of Iowa farmers. In one study, increased chromosomal aberrations were reproted

in agriculture workers exposed to atrazine. Based on available data, no high risk subpopulation has been identified for exposure to atrazine.

Atrazine may interfere with nucleic acid metabolism. It inhibited the *in vivo* incorporation of radiolabeled formate in purines of ascites cells of BALB/c mice injected with the pesticide and the *in vitro* incorporation of radiolabeled precursors of RNA, DNA, and protein into ascites tumor cells. Atrazine also exerted an effect on glycogen metabolism in rats and significantly increased *in vitro* glucagan-stimulated cyclic adenoline monophosphate levels in isolated hepatocytes.

No suitable information was found in the available literature for determination of the One-day Health Advisory (HA). Consequently, the Ten-day HA value of 100 ug/L was used as a conservative estimate of the One-day HA. A No-Observed-Adverse-Effect Level (NOAEL) of 1 mg/kg/day, identified in a developmental toxicity study in rabbits, was used to calculate the Ten-day HA. Since no suitable information was found upon which to base a Longer-term HA, it is recommended that the adjusted Drinking Water Equivalent Level (DWEL) for a 10-kg child of 50 ug/L and the DWEL for a 70-kg adult of 200 ug/L be used at this time as conservative estimates of the Longer-term HA values. A NOAEL of 0.5 mg/kg/day based on reproductive paremeters, identified in a 2-generation feeding study in rats, was used to calculate the Reference Dose (RfD) and the DWEL for atrazine. Using this value, the RfD was estimated to be 0.005 mg/kg/day and the DWEL to be 200 ug/L off.

II. PHYSICAL AND CHEMICAL PROPERTIES

A. GENERAL PROPERTIES

Atrazine 2-chloro-4-ethylamino-6-isopropylamino-s-triazine, is moderately soluble in water (70 mg/L at 22°C) and is readily soluble in most organic solvents. Some physical and chemical properties of atrazine are listed in Table II-1.

B. MANUFACTURE, USES, AND OCCURRENCE

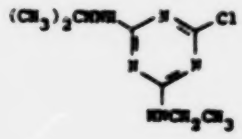
1. Synthesis of Atrazine

Atrazine and other s-triazine herbicides are formed by trimerization of cyanogen chloride followed by reaction of the resultant cyanuric chloride with alkylamines (Figure II-1). Replacement of the first chlorine atom is carried out with the temperature maintained between -15° and 0°C in the presence of an acid acceptor; this may be either a second mole of amine or an equivalent quantity of sodium hydroxide, sodium carbonate, or sodium bicarbonate. Substitution of the second chlorine atom is carried out with the temperature raised to 20° to 60°C and the quantities of amine and acid acceptor doubled. The method reportedly gives high yields of excellent quality product (Gysin and Knusli, 1960; Esser et al., 1975; Melnikov, 1971).

2. Uses of Atrazine

Atrazine was introduced by J.R. Geigy in 1958 for use as a pre- and postemergent herbicide. It rapidly became popular for weed control in corn, sorghum, rangeland, macadamia orchards, pineapples, turf grass sod, and sugarcane, and has been one of the most widely used herbicides in the United States since its introduction (Wolfe et al., 1976; USDA, 1984). As of 1982,

Table II-1. Physical and Chemical Properties of Atrazine (2-chloro-4-ethylamino-6-isopropylamino-s-triazine)

Property		Value
Physical state		White, crystalline
Chemical Abstracts (CAS) Registry No.		1912-24-9
Registry of Toxic Effects of Chemical Substances (RTECS) No.		XY 56000
Synonyms (trade names)		Aatrex, Aatram, Atrasol, Atratol, Bicep, Gesaprim, Primatol, Zeazin
Structure		
Chemical formula		$C_8H_{14}N_5Cl$
Molecular weight		215.7
Ionization constant (pKa)		1.68
Melting point		175°-177°C
Density		1.187 g/cm^3
Stability		Stable in neutral, slightly acidic, or basic solution; hydrolyzed by alkali or mineral acids at higher temperatures
Solubility:	Water	22 ppm at 0°C 70 ppm at 22°C 320 ppm at 85°C
	Methanol	18,000 ppm
	Chloroform	52,000 ppm
	Dimethyl sulfoxide	183,000 ppm
	Ethylacetate	28,000 ppm
	Diethylether	12,000 ppm

SOURCE: Adapted from Bailey and White (1965); Esser et al. (1975); Gunther and Gunther (1970); Hayes (1982); Meister (1987); Melnikov (1971); Weed Science Society of America (1979); Weiss (1980); White-Stevens (1971); Windholz (1983).

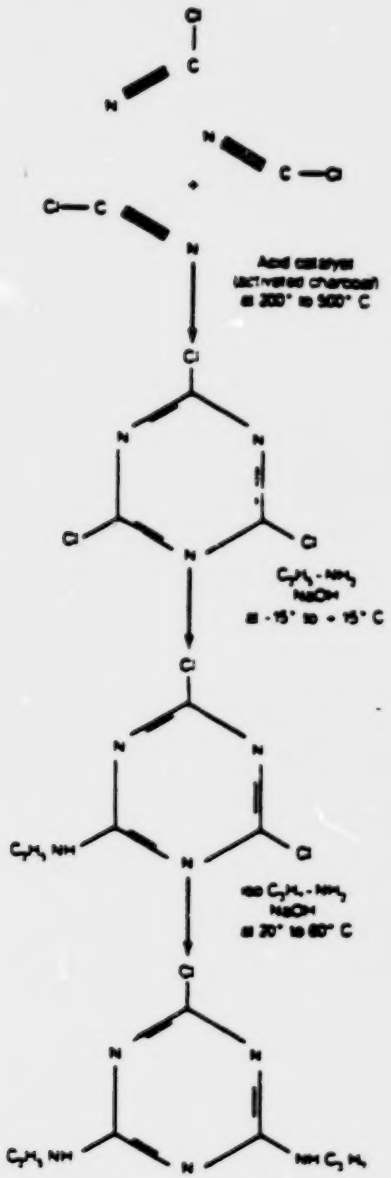


Figure II-1. Atrazine synthesis.

SOURCE: Adapted from Esser et al. (1975).

annual U.S. production of atrazine was reported to be 80.1 million pounds (CEH, 1985).

3. Occurrence of Atrazine

Atrazine has been found in 4,123 of 10,942 surface water samples analyzed and in 343 of 3,208 groundwater samples (STORET, 1988). Samples were collected at 1,659 surface water locations and 2,510 groundwater locations. The 85th percentile of all non-zero samples was 2.3 ug/L in surface water and 1.9 ug/L in groundwater sources. The maximum concentration found was 2,300 ug/L in surface water and 700 ug/L in groundwater. Atrazine was found in surface water of 31 States and in groundwater of 13 States. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET data base. The individual data points retrieved were used as they came from STORET, and their validity has not been confirmed. STORET data are often not valid when individual numbers are used outside the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Atrazine also has been found in groundwater in Pennsylvania, Iowa, Nebraska, Wisconsin, and Maryland; typical positives were 0.3 to 3 ppb (Cohen et al., 1986).

C. ENVIRONMENTAL STABILITY AND FATE

Atrazine is stable in solid form and in neutral solutions (Hayes, 1982) but undergoes microbial degradation and photodecomposition in soil (Harris et al., 1968; LeBaron, 1970). The latter may not play a significant role under natural conditions, however, due to other environmental factors, such as

leaching below light-penetrating zones in the soil (USDA, 1984). At application rates of 2 kg/acre or below, residual phytotoxicity usually persists for 3 to 12 months. Moist, warm soils, which favor microbial activity, are conducive to decreased persistence, and dry or cold soils are associated with increased persistence (Harris and Warren, 1964; Talbert and Fletchall, 1964, 1965; Harris et al., 1968; Esser et al., 1975).

An aerobic soil metabolism study in Lakeland sandy loam, Hagerstown silty clay loam, and Wehadkee silt-loam soils determined that atrazine was converted to hydroxyatrazine (in 8 weeks) at rates of 38, 40, and 47% of the amount applied, respectively (Harris, 1967). In addition, Beynon et al. (1972) identified two more degradates of atrazine, which were deisopropylated atrazine and deethylated atrazine in a sandy loam study.

Soil thin-layer chromatography (TLC), column leaching, and adsorption/desorption batch equilibrium studies revealed that atrazine is moderately to highly mobile in soils ranging in texture from clay to gravelly sand. Soil TLC further revealed atrazine to be intermediately mobile in loam, sandy clay loam, clay-loam, silt-loam, silty clay-loam, and silty clay soils, and mobile in sandy loam soils (Helling, 1971). Soil column studies showed atrazine to be mobile in sand, fine sandy loam, silt-loam, and loam; intermediately mobile in sand, silty-clay loam, and sandy loam soils; and slightly low to intermediately mobile in clay-loam soils (Ivey and Andrews, 1964, 1965; Weidner, 1974; Lavy, 1974).

The adsorption coefficients for atrazine vary in soils, ranging from 0.6 in sandy loam to more than 21 in peat (Talbert and Fletchall, 1965; Weidner, 1974; Lavy, 1974).

Hurle and Kibler (1976) studied the effect of water-holding capacity on the rate of degradation and found a half-life for atrazine of more than 125, 37, and 36 days in sandy soil held at 4, 35, and 70% water-holding capacity, respectively.

Warnock and Leary (1978), Portnoy (1978), and Buchanan and Hiltbold (1973) discuss the half-lives of atrazine and atrazine phytotoxic residues, which range from 20 to 167 days.

In a loam to silt-loam soil, atrazine phytotoxic residues persisted for more than 1 year after application and were detected at maximum depth samples of 30 to 42 inches. Atrazine phytotoxic residues also persisted in silty clay-loam and loam soils 16 months after application and were detected at depths of 12 to 24 inches (Darwent and Behrens, 1968; Buchanan and Hiltbold, 1973).

In aquatic field conditions, the dissipation of atrazine was due to leaching and dilution by irrigation water. Atrazine residues persisted for 3 years in soil and at the sides and bottoms of irrigation ditches, and they were detected at the maximum sample depth of 67.5 to 90 cm (Smith et al., 1975).

Atrazine has demonstrated the potential to be converted to an N-nitrosamine. This finding has created interest for two reasons. First, it is common for atrazine to be applied concurrently with nitrogen-containing fertilizers, thus providing the potential for nitrosamine formation in the fields. Second, nitrosamine formation may take place in the stomach from atrazine present in drinking water (Mirvish, 1975; Wolfe et al., 1976).

Degradation of atrazine to CO_2 appeared minimal as carbon dioxide production was generally slow in several anaerobic soils: sandy loam, clay-loam, loamy sand, and silt-loam soils (Wolf and Martin, 1975; Goswami and Green,

1971; Lavey et al., 1973). [14C]Atrazine was stable in aerobic groundwater samples incubated without light for 15 months at 10° or 25°C (Weidner, 1974).

Ciba-Geigy (1988) recently submitted comments on the results of its studies on the environmental fate of atrazine. Results of laboratory degradation studies showed that atrazine is relatively stable in the aquatic medium under environmental pH conditions. This summary also indicated that atrazine degraded in soil by photolysis and microbial processes. The products of degradation are dealkylated metabolites, hydroxyatrazine, and nonextractable (bound) residues. Atrazine and the dealkylated metabolites are relatively mobile, whereas hydroxyatrazine is immobile.

Ciba-Geigy (1988) also indicated that field dissipation studies conducted in California, Minnesota, and Tennessee show no leaching of atrazine and metabolites below 6 to 12 inches of soil depth. The half-lives of atrazine in soil ranged from 20 to 101 days, except in Minnesota soil, where degradation was slow. A forestry degradation study conducted in Oregon showed no adverse effects on either terrestrial or aquatic environments. Bioconcentration studies also have shown low potential for bioaccummulation.

The USDA (1984) reported that atrazine is absorbed primarily by plant roots and translocated to all aboveground parts; it accumulates in the margins of leaves. Atrazine has a low tendency to accumulate in animal tissues. When bioaccumulation occurs, atrazine is readily converted to nontoxic metabolites that are rapidly excreted by the kidney.

D. SUMMARY

Atrazine is 2-chloro-4-ethylamino-6-isopropylamino-s-triazine. It has moderate solubility in water (70 mg/L at 22°C) and is readily soluble in most

organic solvents. Atrazine is widely used as a selective herbicide for the control of weeds in corn, sorghum, rangeland, sugarcane, macadamia orchards, pineapples, and turf grass sod.

Atrazine is stable in solid form or in neutral solutions, but it is subject to breakdown in soil by microbial action and photodecomposition. The products of degradation are dealkylated metabolites, hydroxyatrazine, and nonextractable (bound) residues. Unlike atrazine and dealkylated metabolites, hydroxyatrazine is immobile. The half-lives of atrazine in soil ranged from 20 to 101 days. Atrazine has low potential for bioaccumulation. Under typical conditions, residual phytotoxicity persists for 3 to 12 months.

III. TOXICOKINETICS

A. ABSORPTION

Atrazine appears to be readily absorbed from the gastrointestinal tract of animals. Bakke et al. (1972) administered single doses of [^{14}C]ring-labeled atrazine in ethanol to rats by stomach tube. Fourteen rats (310 to 420 g) each received 0.53 mg of [^{14}C]atrazine containing 3.54 uCi of ^{14}C. Urine and feces were collected daily, and tissues were collected for analysis of radioactivity following sacrifice at 2, 4, and 8 days (four rats in each group). Total fecal excretion after 72 hours was 20.3% of the administered radioactivity, the remainder being excreted in the urine (65.5%) or retained in tissues (15.8%). This indicates that at least 80% of the dose was absorbed.

The metabolic disposition of [^{14}C]atrazine also was studied in three groups of rats (five males and five females/group) following administration of a single oral dose of test material (Ciba-Geigy, 1988). One group of animals was dosed at a rate of 1 mg/kg, and a second was dosed at rate of 100 mg/kg. The third was dosed at a rate of 1 mg/kg following a 14-day period of dosing with nonlabeled material at the same rate (1 mg/kg/day). The elimination of radiolabel in urine and feces was monitored over a 7-day period. Data were compared on the basis of sex, dose rate, and pretreatment regimen. Approximately 74 and 19% of the dose were eliminated in the urine and feces, respectively, within 7 days after administration of the radioactive compounds. No sex-, treatment-, or pretreatment-based differences were observed. In fact, consistent urine:feces excretion ratios over the 1- to 100-mg/kg body weight dosage range suggested that absorption of the administered [^{14}C]atrazine was complete. The data were comparable to the data of Bakke et al. (1972) and indicated that about 80% of the original dose was absorbed.

In a dermal absorption study performed by Ciba-Geigy (1983a), male and female Harlan Sprague-Dawley rats, weighing approximately 200 g, were treated dermally with [^{14}C]atrazine (specific activity 17.2 uCi/mg, dissolved in tetrahydrofuran and applied to a 1.5 cm^2 area of the shaved skin at a total volume of 15 to 20 ug/L) at a dose level of 0.25 mg/kg. Approximately 70% of the applied dose was absorbed in 72 hours, resulting in a half-life absorption of approximately 41 hours for both sexes.

B. DISTRIBUTION

Bakke et al. (1972) administered single oral doses of 0.53 mg of [^{14}C]ring-labeled atrazine (in ethanol) to 14 rats by stomach tube. Groups of four rats were sacrificed at 2, 4, and 8 days after dosing, and tissue distribution of radioactivity was determined (Table III-1). Tissues from the liver, kidney, and lung contained the highest levels of radioactivity, and fat and muscle had the lowest.

In a subchronic exposure study, six groups of two female Sprague-Dawley Charles River CD albino rats were dosed daily for 10 consecutive days at rates of 1, 3, 7, 10, 50, or 100 mg [^{14}C]atrazine/kg (Ciba-Geigy, 1988). Tissue concentrations varied in a less than direct proportion to dose rate. In all cases, the highest residues (0.6% or less of the total dose) were found in the red blood cells (RBCs) and liver; other tissues contained less than 0.25% of the total dose. Both total mammary (pectoral and inguinal) concentrations and total tissue (mammary, pituitary, liver, ovary, brain, and kidney) concentrations declined exponentially following cessation of dosing. Tissue concentrations 3 hours after the tenth dose were linearly related to plasma concentrations obtained at the same time point for the dosage range of 1 to 100 mg/kg. Tissue concentrations 72 hours after the tenth dose were significantly lower (27%) and

Table III-1. Radioactivity Detected in Rat Tissues After a Single Dose of [^{14}C]Ring-Labeled Atrazine

Time of sacrifice (days)	Tissue residues[a]							
	Liver	Brain	Heart	Lung	Kidney	Digestive tract	Omental fat	Leg muscle
2	3.5	1.6	2.5	3.0	4.0	5.8	0.5	0.6
4	2.6	1.4	1.6	2.3	2.3	0.9	0.1	0.5
8	1.7	1.1	1.4	2.0	1.7	0.9	0.1	0.5

[a] Average of tissues from four rats. Values are expressed as ppm atrazine (^{14}C-equivalent) on a freeze-dried tissue weight basis.

SOURCE: Adapted from Bakke et al. (1972).

also linearly related to plasma concentrations. Comparison of tissue concentrations 3 hours and 72 hours after cessation of dosing indicates a longer residence time for radioactivity in tissues other than plasma. The whole-body half-life was approximately 1-1/2 days.

Based on plasma concentrations, the apparent volume of body distribution was 4.15 L/kg body weight. An apparent volume of body distribution for RBCs, 0.70 L/kg body weight, supports extensive covalent binding to red blood cells with a half-life of 5 to 8 days, consistent with the lifespan of rat RBCs (45 to 56 days). A steady-state RBC concentration was estimated to be achieved only after 30 days of daily dosing. In a review of the Ciba-Geigy (1988) study, Hauswirth (1988) concluded that atrazine and/or its metabolites appear to bind to RBCs, but accumulation in other tissues does not appear to occur.

In a kinetic phase of the Ciba-Geigy (1983a) study on dermal absorption of atrazine, four male and four female Harlan Sprague-Dawley rats were sacrificed at 2, 4, 8, 24, or 48 hours after dermal application of 0.25 mg [^{14}C]atrazine/kg body weight for estimation of tissue distribution. The highest levels were measured in liver and muscle at all time points examined, with the radioactivity reaching a peak of 2.1% in muscle and 0.5% in liver at the 8-hour time point.

Khan and Foster (1976) observed that in chickens the hydroxy metabolites of atrazine accumulate in the liver, kidney, heart, and lung. Residues of both 2-chloro and 2-hydroxy moieties were found in chicken gizzard, intestine, leg muscle, breast muscle, and abdominal fat.

C. METABOLISM

Metabolism of atrazine proceeds primarily via N-dealkylation. Bakke et al. (1972) administered a single oral dose of 0.53 or 5.5 mg [^{14}C]ring-labeled

atrazine to rats by stomach tube. Less than 0.1% of the radioactivity appeared as $^{14}CO_2$ in expired air, indicating that the triazine ring did not undergo complete metabolic breakdown. Most of the radioactivity derived from the atrazine was recovered in the urine of the treated rats (65.5% in 72 hours). At least 19 radioactive compounds were determined to be present in the urine by ion-exchange chromatography, gas chromatography, and mass spectrometry (Table III-2). Four of these compounds, constituting approximately 47% of the urinary radioactivity, were identified as 2-hydroxyatrazine, its two mono-N-dealkylated metabolites, and ammeline (4,6-diamino-s-triazine-2-ol). None of the urinary metabolites identified contained the 2-chloro moiety; however, this may have been due to hydrolytic displacement of the 2-chloro group on the ion-exchange column during isolation.

Bonme and Bar (1967) isolated and identified five rat urinary metabolites of atrazine. These were identified as the two mono-dealkylated metabolites of atrazine, the corresponding carboxylic acid derivatives, and the di-dealkylated derivative (Figure III-1). All of these metabolites contained the 2-chloro group. The discrepancy between the results of Bakke et al. (1972) and Bonme and Bar (1967) may be attributable to the isolation technique used by the former investigators, which may have caused hydrolytic displacement of the 2-chloro group.

Ciba-Geigy (1988) indicated that when five female rats were given a single oral dose of 100 mg [^{14}C]atrazine/kg for the purpose of metabolite isolation and identification, experimental evidence supported a metabolic pathway dominated by oxidative removal of the alkyl side chains with 2-chloro-4,6-diamino-s-triazine being the major metabolite. The carbon-chlorine bond on the second carbon was stable to enzymatic hydrolysis but was subject to conjugation via the action

Table III-2. Recovery and Chromatographic Characterization of Metabolites Recovered From the Urine of Rats Dosed With [^{14}C]Ring-Labeled Atrazine

Ion-exchange chromatography fraction No.	% of radioactivity in the urine		R_f[b]	GLC elution temperature (°C)
	0.53 mg[a]	5.5 mg[a]		
1, 2, 3	3.0	5.7		
4, 5	2.0	<1		
6	1.0	2.0		
7	5.2	5.5	Origin	167 217 (212)[c] 230
8	4.1	2.6		
9	2.4	3.7		
10	3.0	1.9		
11, 12	7.7	5.6	0.35	205
13	33.0	54.0	Origin	166
14	3.6	1.7		
15	2.4	0.8		
16, 17, 18	12.7	8.5	0.34 0.5	178 177
19	4.1	0.9	0.75	186
TOTAL	84.2	92.9		

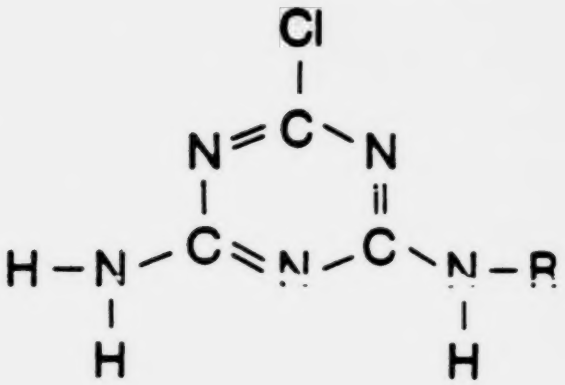
[a]Doses given to each rat.
[b]Paper chromatography.
[c]GLC elution temperature of the methylated and silanized metabolite.

SOURCE: Adapted from Bakke et al. (1972).

of glutathione-S-transferase. Sulfur-containing metabolites were converted to 2-sulfhydryl-s-triazines, which in turn were subject to methylation followed by oxidation to the corresponding S-oxides. Oxidation of primary positions of the alkyl side chains to carboxyl function appeared to be a minor alternative metabolic route.

Hauswirth (1988) evaluated the rat metabolism studies discussed above, she concluded that there was sufficient data to show that in the female rat, dechlorination of the triazine ring and N-dealkylation were the major metabolic pathways. Hauswirth also agreed with Ciba-Geigy (1988) that oxidation of the alkyl substituents appears to be a minor and secondary metabolic route. However, Hauswirth (1988) indicated that the above data did not identify the fecal metabolites in male and female rats, and that the urinary metabolites in male rats also need to be identified unless an acceptable rationale can be given for the formation of the same metabolites in male and female rats.

Dauterman and Muecke (1974) studied the metabolism of atrazine by liver subcellular fractions obtained from male RAI rats (150 to 170 g). Metabolites were isolated using several thin-layer chromatographic systems. Dealkylation of atrazine occurred in the microsomal fraction and was found to be NADPH-dependent. Atrazine produced a type I spectral change when added to mouse liver microsomes (Mailman and Hodgson, 1972), suggesting it was a substrate for the cytochrome P-450-dependent microsomal monooxygenase system. Dauterman and Muecke (1974) observed that the isopropyl group of atrazine was more readily removed than the ethyl group. The di-dealkylated derivative was also identified as a metabolite. Conjugation with glutathione occurred in the soluble fraction of the rat liver. Most of the chloro-s-triazines studied formed conjugates with glutathione, but dealkylation reactions predominated



Metabolite	R
1	-H
2	$-C_2H_5$
3	$-CH(CH_3)_2$
4	$-CH_2COOH$
5	$-CH(CH_3)COOH$

Figure III-1. Metabolites of atrazine isolated from rat urine.

SOURCE: Adapted from Bohme and Bar (1967).

over conjugation. Subsequent studies by Guddewar and Dauterman (1979) of *in vitro* metabolism of atrazine with a mouse liver glutathione-S-transferase preparation demonstrated that a chloro group at the 2 position was essential for conjugation, and that the rate of conjugation decreased with decreasing alkyl substitution. There was no indication from the studies of Dauterman and Muecke that atrazine or any of its dealkylated metabolites was dechlorinated *in vitro* by rat liver. Figure III-2 illustrates the pathways of atrazine metabolism by rat liver proposed by Dauterman and Muecke.

Bradway and Moseman (1982) administered oil suspensions of atrazine (50, 5, 0.5, or 0.005 mg) daily for 3 days to male Charles River rats (300 g) and separated the urinary metabolites by gas chromatography. The di-dealkylated derivative (2-chloro-4,6-diamino-*s*-triazine) was the major urinary metabolite, with lesser amounts of the two mono-N-dealkylated derivatives. In contrast to the *in vitro* observations of Dauterman and Muecke (1974), they obtained more of the deethylated metabolite than the deisopropylated derivative, suggesting that metabolism *in vivo* differs somewhat from that predicted by *in vitro* studies with subcellular fractions.

The *in vivo* metabolism of atrazine in Pittman-Moore mini-pigs was studied by Erickson et al. (1979). Animals that were 2 to 4 months old (14 to 23 kg) were dosed with 0.1 g of commercial atrazine 80W in ethanol by stomach tube while under pentobarbital anesthesia. Urine samples were collected for 46 hours from a drain in the floor of the metabolism cages. Metabolites were separated and identified by gas chromatography and mass spectrometry. Excretion was essentially complete within 24 hours. The major compound identified in urine was the parent compound (atrazine), and deethylatrazine was the principal urinary metabolite.

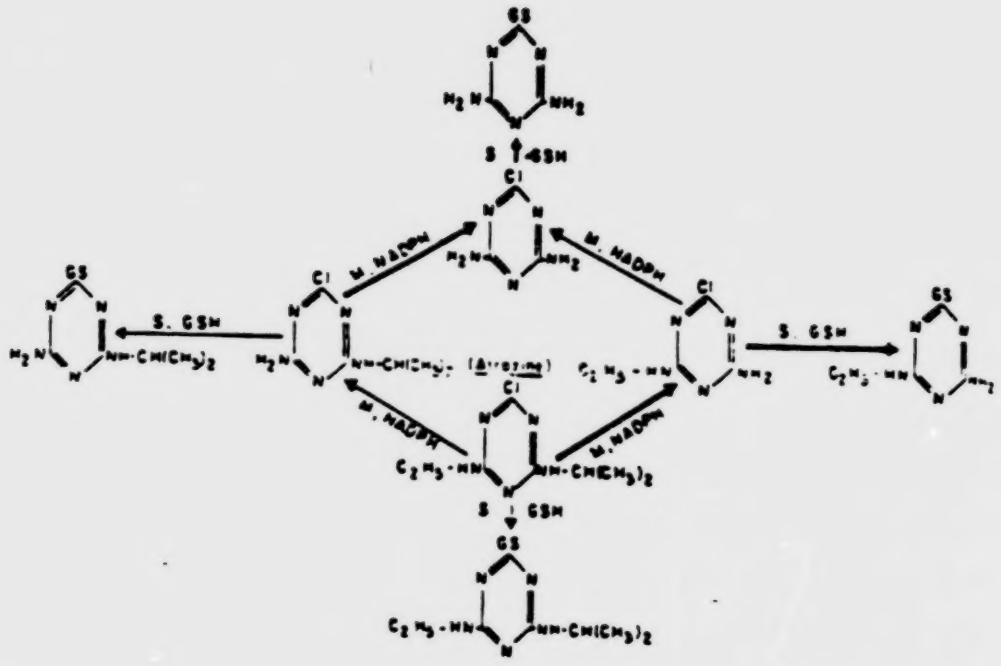


Figure III-2. Proposed pathways for the metabolism of atrazine by rat liver *in vitro*.

M = microsomal fraction.
S = 100,000 g supernatant.
Heavy lines = major pathway.

SOURCE: Adapted from Dauterman and Muecke (1974).

In the guidane for reyistration of atrazine containing pesticide products, the agency has suggested additional research concerning atrazine metabolism to be conducted although the available studies on metabolism are acceptable (U.S. EPA, 1989). The issues need to be addressed are: 1) Identification of fecal metaoblites in the male and the female rat. 2) Identification of urinary metabolites in the male rat unless an acceptable rationale can be given that both sexes produce the same metabolaites. 3) An explanation for the observed differences between the two studies for the percentage elimination of ratioactivity in the urine (50 to 75%) and feces (20 to 50%) of female rats given a single oral dose of 100 mg/kg of [14_C]atrazine (details of these two studies are presented in Section D. Excretion).

D. EXCRETION

The urine appears to be the principal route of atrazine excretion in animals. Following the intragastric administration of 0.5-mg doses of [^{14}C]ring-labeled atrazine to rats, Bakke et al. (1972) reported that 65.5% of the radioactivity was excreted in the urine in 72 hours. Total fecal excretion after 72 hours was 20.3% of the radioactivity, and less than 0.1% appeared as $^{14}CO_2$ in expired air. A total of 85 to 95% of the urinary radioactivity appeared within the first 24 hours after dosing, indicating rapid clearance.

Similar data were discussed by Ciba-Geigy (1988) where the administration of single oral doses of 1 or 100 mg [^{14}C]atrazine/kg to groups of five male and five female Sprague-Dawley rats gave similar results to the above findings. More than 90% of the administered atrazine was excreted, with approximately 74 and 19% of the ^{14}C dose recovered in the urine and feces, respectively, within 7 days after dosing. The kinetics of elimination showed the same consistency

as did the routes of elimination; data in all cases best fit a first-order elimination from a two-compartment open system. A whole-body half-life of elimination was determined as 31.3±2.8 hours. Ciba-Geigy (1988) reported no sex- or dose-related differences in elimination of radioactivity.

Hauswirth (1988) reported, however, that the results discussed by Ciba-Geigy (1988) showed that approximately 50% of the administered radioactivity was found in the urine and 50% in the feces of female rats given a single oral dose of 100 mg [^{14}C]atrazine/kg. Thus, the rates of ^{14}C elimination account for 50 to 75% in urine and 20 to 50% in feces. The observed differences reported in the above two studies in the elimination of radioactivity in feces and urine need to be explained by additional studies (U.S. EPA, 1989).

Ciba-Geigy (1983b) studied the excretion rate of [^{14}C]atrazine from Harlan Sprague-Dawley rats dermally dosed with atrazine dissolved in tetrahydrofuran at levels of 0.025, 0.25, 2.5, or 5.0 mg/ kg. Urine and feces were collected from all animals at 24-hour intervals for 144 hours. Most of the radioactivity for all dose levels was excreted in the urine within 48 hours after administration, ranging from 37% for the lowest dose to 59% for the highest. Excretion in the feces was about 15% at the lowest dose levels and between 20 and 21% for all other dose levels. Combined cumulative excretion in 144 hours for urine and feces was 52% at the lowest dose and 70 to 80% at all other doses.

Dauterman and Muecke (1974) have reported that atrazine metabolites are conjugated with glutathione to yield a mercapturic acid in the urine. The studies of Foster et al. (1979) in chicken liver homogenates also indicate that atrazine metabolism involves glutathione.

E. BIOACCUMULATION AND RETENTION

No studies were found that provided data on tissue retention or accumulation of atrazine during continued exposure. Bakke et al. (1972) measured levels of ^{14}C label in rat tissues at 2, 4, or 8 days after a single oral dose of [^{14}C]atrazine. After 72 hours, 15.8% of the radioactivity administered was still present in body tissues, and these tissue levels were found to be decreasing rather slowly (see Table III-1), suggesting that repeated dosing might result in tissue accumulation. It was not determined if the retained radioactivity was still present in the form of intact atrazine or metabolite(s), and, if the latter, whether the metabolite(s) were covalently bound to biomaterials.

F. SUMMARY

The toxicokinetics of atrazine have not been extensively studied. In one study in rats given 0.53 mg of radiolabeled atrazine by stomach tube, absorption was about 80%. Absorbed atrazine was found to be distributed throughout the body, with radioactivity levels in the kidney, liver, and lung being higher than levels in fat and muscle. Ingested atrazine is excreted primarily via the urine. The urine accounted for 65.5% of the radioactivity from an ingested dose of radiolabeled atrazine and the feces 20.3%, with 15.8% remaining in the tissues after 72 hours. Results of the single oral study in rats indicated that the urine was the preferred route of excretion representing approximately 74% of the dose, regardless of sex, dose rate, or pretreatment regimen. Mean fecal excretion was 19%. A whole-body half-life of elimination was determined to be 31.3 ± 2.8 hours. A 10-day repeated dosing study gave consistent urine:feces excretion ratios, (about 4:1 over the 1- to 100-mg/kg dose range, suggesting that the absorption of administered [^{14}C]atrazine was

complete. (A review of another similar study, however, indicated that eliminated radioactivity was distributed equally between urine and feces following administration of single oral doses of 100 mg [^{14}C]atrazine/kg/day to rats.) Red blood cells exhibited the highest tissue levels of radioactivity (average 0.6% of total dose); other organs contained less than 0.25% of the total dose. Subchronic administration does not alter the patterns or the first-order kinetics of [^{14}C]atrazine observed for single dose.

Dechlorination of the triazine ring and N-dealkylation are the major metabolic pathways for atrazine, with 2-chloro-4,6-diamino-s-triazine being the major metabolite. Oxidation of the alkyl substituents appears to be a minor and secondary metabolic route. Conjugation of atrazine and its metabolites with glutathione by liver cytosol has been demonstrated in vitro, and atrazine metabolites conjugated with glutathione to yield mercapturic acids are found in the urine. In chickens, the hydroxy metabolites of atrazine accumulate in tissues, and residues of both 2-chloro and 2-hydroxy moieties have been found in a number of chicken tissues. Studies are required to characterize the elimination products of atrazine in feces of male and female rats and urinary metabolites in the male rat. Additionally, the reason for the observed discrepancy in the elimination of radioactivity in urine and feces, in two studies requires quantification.

Atrazine is slowly absorbed from rat skin; approximately 70% of the applied dose is absorbed in 72 hours. Tissue levels are highest in muscle and liver at all times following dermal absorption in rats, and most of the absorbed dose is excreted within 48 hours, mainly in the urine and, to a lesser extent, in the feces.

IV. HUMAN EXPOSURE

Information on human exposure is presented in the appendix portion of this doucment.

V. HEALTH EFFECTS IN ANIMALS

A. SHORT-TERM EXPOSURE

1. Letnality

A summary of oral LD_{50} and LD_{100} values for atrazine in various species is given in Table V-1. The LD_{50} values recorded for rats range from 672 mg/kg (Gaines and Linder, 1986) to 3,000 mg/kg (Bashmurin, 1974). In rats administered atrazine intraperitoneally, an LD_{50} of 125 mg/kg and an LD_{100} of 280 mg/kg have been reported (Gznetotskii et al., 1977). Acute oral studies reflected an LD_{50} of 1,869 mg/kg in rats and an LD_{50} >3,000 mg/kg in mice (Ciba-Geigy, 1988).

Gaines and Linder (1986) determined the LD_{50} value for atrazine by both oral and dermal routes in adult male, adult female, and weanling Sherman rats (weights not given). A minimum of 10 animals and four dosage levels was used for each LD_{50} calculation. Technical-grade atrazine was suspended in peanut oil for oral dosing by stomach tube, or in propylene glycol for dermal application. As shown in Table V-1, the oral LD_{50} values of 737 mg/kg for adult males and of 672 mg/kg for adult females are lower than the values recorded in earlier studies. Atrazine was less toxic to weanling rats (LD_{50} = 2,310 mg/kg) by the oral route, which may be a reflection of the difference in the metabolic capability of weanling rats as compared to adult rats, with an adult/weanling LD_{50} ratio of 0.32. Adult rats of both sexes showed an LD_{50} greater than 2,500 mg/kg by the dermal route.

In a report available only in abstract form, Molnar (1971) administered 600 or 3,000 mg atrazine/kg (almost twice the LD_{50}) intragastrically to rats (number not specified). Six percent of the rats died within 6 hours, and 25% of those remaining died within 24 hours (dose not indicated). The rats that

Table V-1. Summary of Oral Lethality Data on Atrazine

Species	Age/weight	Sex	Parameter	Value (mg/kg)	Reference
Mouse	--[a]	--	LD_{50}	1,750	Bashmurin (1974)
Mouse	--	--	LD_{50}	3,000	Ciba-Geigy (1988)
Hamster	6 weeks	M/F	LD_{50}	1,000	Cabral et al. (1979)
Rat	--	--	LD_{50}	3,000	Bashmurin (1974)
Rat	--	--	LD_{100}	3,000	Gzhetotskii et al. (1977)
Rat	--	--	LD_{50}	1,400	Gzhetotskii et al. (1977)
Rat	210-275 g	M	LD_{50}	1,540	Stillmeadow, Inc. (1980)
Rat	165-210 g	F	LD_{50}	1,380	Stillmeadow, Inc. (1980)
Rat	--	--	LD_{50}	2,030	Instituto Di Ricerche (1976)
Rat	--	--	LD_{50}	2,850	Consultox Laboratories Ltd. (1974)
Rat	--	--	LD_{50}	2,330	Hill Top Research, Inc. (1980)
Rat	>90 days	M	LD_{50}	737	Gaines and Linder (1986)
Rat	>90 days	F	LD_{50}	672	Gaines and Linder (1986)
Rat	4-6 weeks	M	LD_{50}	2,310	Gaines and Linder (1986)
Rat	--	--	LD_{50}	1,869	Ciba-Geigy (1988)

[a] Not reported.

died during the first day exhibited lung edema with extensive hemorrhagic foci, cardiac dilation, and microscopic hemorrhages in the liver and spleen. Rats that died during the second day had hemorrhagic bronchopneumonia and dystrophic changes of the renal tubular mucosa. Rats sacrificed after 24 hours had cerebral edema and histochemical alterations in the lung, liver, and brain.

Palmer and Radeleff (1964) carried out lethality studies using predominantly Delaine-breed sheep and mixed-breed, dairy-type cattle (one animal/group). Atrazine was administered orally either in solution or in a gelatin capsule. Two doses of 250 mg atrazine/kg caused death in both sheep and cattle. Sixteen daily doses of 100 mg/kg were lethal to one sheep. At necropsy, degeneration and discoloration of the adrenal glands and congestion in the lungs, liver, and kidneys were observed.

An acute dermal LD_{50} value of 7.55 g/kg for technical-grade atrazine applied to rabbits was reported by Frear (1969). No other details were given.

2. Other Effects

A 28-day study was conducted in which groups of five male and five female mice received atrazine in their feed at concentrations of 0, 10, 30, 100, 300, 1,000, 3,000, 10,000, or 30,000 ppm (0, 1.5, 4.5, 15, 45, 150, 450, 1,500, or 4,500 mg/kg/day, respectively) (IBT, 1976). At doses up to 1,000 ppm (150 mg/kg/day), atrazine had no effect on mortality or on any of the other parameters evaluated. The 3,000-ppm (450 mg/kg/day) dose resulted in death in 2 of 10 mice, but there was no evidence of gross pathology. At the two highest doses, decreases in food intake and body weight were observed, as well as tremors, muscle weakness, and increased mortality.

Bashmurin (1974) reported that a single oral administration of 100 mg/kg of atrazine to cats had a hypotensive effect, and that a similar dose in dogs was antidiuretic and resulted in decreased serum cholinesterase (ChE) activity. No other details were reported. Atrazine is not an organophosphate; therefore, its effect on ChE may not be similar to the mechanism of ChE inhibition by organophosphates.

The effects of feeding atrazine to sheep and cattle were evaluated by the Geigy Chemical Corporation (1961). Sheep were administered 50, 100, or 400 mg atrazine/kg/day (one animal/dose). The sheep receiving 400 mg/kg/day died on the second day, the sheep receiving 100 mg/kg/day died on day 16, and the sheep receiving the lowest dose survived 28 days but lost weight. When sheep (one animal per dose level) were administered 1.0, 5, or 25 mg atrazine/kg/day, 6 days per week for 5 weeks, no deaths or gross pathology were recorded. Similarly, dietary doses of 10, 30, or 100 ppm (0.4, 1.2, or 4.0 mg/kg/day, respectively) for 28 days had no adverse effects on sheep, and dietary doses of 3, 15, or 100 ppm (0.045, 0.23, or 1.5 mg/kg/day, respectively) for 21 days had no effect on food intake, milk production, or on the overall physical condition of the cattle.

Palmer and Radeleff (1969) dosed cattle and sheep orally with atrazine 80W (Geigy), administering the material either as an aqueous solution by syringe or as a powder in a gelatin capsule. Cattle received 10 or 25 mg/kg per dose in 10 doses. Sheep received 5, 10, 25, 50, or 100 mg/kg per dose in 10 doses. The numbers of animals in each dosage group were not stated, and the use of controls was not indicated. Observed effects included muscular spasms of varying intensity in the hindquarters, a stilted gait and stance, and anorexia at all dose levels in sheep and at 25 mg/kg in cattle. Necropsy revealed

petechiae on the surface of the epicardium, and congestion of the kidneys, liver, and lungs. Enlarged adrenals were noted in some of the animals. A short-term Lowest-Observed-Adverse-Effect Level (LOAEL) of 5 mg/kg/day in sheep and a No-Observed-Adverse-Effect Level (NOAEL) of 10 mg/kg/day in cattle can be identified from this study.

Johnson et al. (1972) fed atrazine-treated hay to calves and sheep in an experiment designed to simulate natural grazing conditions. Six yearling ewes (45 to 53 kg) and six Holstein-Friesien calves (105 to 165 kg) were divided into three groups of two ewes and two calves each, and for 25 days, were fed hay derived from either untreated grass or from grass sprayed with atrazine at rates of either 22.5 or 44.9 kg/hectare. The average daily intake of atrazine in the two dose groups was 31 or 42 mg/kg/day in sheep and 20 or 37 mg/kg/day in calves. No gross signs of adverse effects were observed in either species. Body weights were not different from the control, and various clinical tests were within normal limits. No demonstrable histopathologic changes were observed in the liver, kidney, pancreas, spleen, adrenal glands, thyroid gland, lung, stomach, small or large intestine, or cardiac muscle tissue.

Since the primary route of elimination of ingested atrazine is in urine, via the kidney (Bakke et al., 1972), Santa Maria et al. (1986) evaluated the toxic effects of atrazine on rat renal function. Adult male Wistar rats, divided into groups of 10, received 0, 100, 200, 400, or 600 mg atrazine/kg, administered with gum arabic by oral intubation, for 14 days. Urine was collected daily for analysis of constituents. Results showed that subacute atrazine exposure in rats significantly increased the elimination of sodium, potassium, and chloride, with a dose-related degree of increase. The increased elimination of electrolytes was attributed to an alteration in the resorption

mechanism in the renal tubules. Except for the group treated with atrazine at 100 mg, there was a significant decrease in creatinine clearance in atrazine-exposed rats compared to controls, which may be attributed to a decrease in the glomerular filtration rate. A significant dose-related increase in urine protein levels was observed at all levels in atrazine-exposed rats, suggesting that lesions are produced on the glomerular membrane causing either an increase in permeability for plasma protein or a subsequent decrease in reabsorption in renal tubules. The overall results indicate that exposure to atrazine significantly affects kidney function.

Castano et al. (1982), investigating possible neurotoxic effects of atrazine, determined the effect of atrazine administration in rats on the morphology of sciatic nerve fibers. Two groups, each consisting of 14 Sprague-Dawley rats, were treated intraperitoneally with either 20 or 40 mg of atrazine dissolved in dimethyl sulfoxide (DMSO), twice weekly for 1 month. A control group of 12 rats received only DMSO. Half of the animals in each group were sacrificed at the end of treatment; the other half was sacrificed after a recovery period of an additional 30 days. Samples of the sciatic nerve, the spinal ganglia, and the spinal cord were removed for examination by electron microscope. The only change noted was a statistically significant decrease in axonal areas, both in myelinated and unmyelinated fibers, for the group treated with 40 mg of triazine and sacrificed immediately at the end of treatment. After a recovery period of 30 days, axonal areas had returned to normal. Light-microscopic examination of samples of the liver, kidney, lung, and lymph nodes showed no difference between experimental and control animals.

In a primary dermal irritation test in rats, atrazine administered at 2,800 mg/kg produced erythema but no systemic effects (Hayes, 1982). In primary

eye irritation studies, atrazine was described as irritating when applied at an unspecified concentration in rats (Hayes, 1982).

In the guidance for pesticide registration, the agency summarized that atrazine has low to mild acute oral and dermal toxicities. It produces moderate ocular irritation, slight dermal irritation and no dermal sensitization (U.S. EPA, 1989). The agency has suggested that a 21-day dermal toxicity study to be carried out.

Summaries of the acute and short-term effects of atrazine in monogastric animals and ruminants are presented in Tables V-2 and V-3, respectively.

B. LONG-TERM EXPOSURE

Table V-5 summarizes studies on the effects of long-term exposure to atrazine.

In a 91-week oral feeding/oncogenicity study conducted by Ciba-Geigy (1987c), atrazine (97% a.i.) was fed to 5-week-old CD-1 male and female mice weighing 26.8 and 21.0 g, respectively. The mice (60/sex/group) were randomly assigned to five experimental groups. The doses tested were 10, 300, 1,500, and 3,000 ppm, which corresponded to actual mean daily intakes of 1.4, 38.4, 194.0, and 385.7 mg/kg/day for males, and 1.6, 47.9, 246.9, and 482.7 mg/kg/day for females. The dose-related effects in animals consuming 1,500 or 3,000 ppm atrazine included a decrease in the mean body weight gain at 12 and 91 weeks, and decreases in erythrocyte count, hematocrit, and hemoglobin concentrations. In addition, an increase in the incidence of cardiac thrombi was observed in females in the 1,500- and 3,000-ppm exposure groups. Both amyloidosis and cardiac thrombi contributed to the deaths of mice who did not survive to terminal sacrifice (termed as "early death" mice). A statistically significant increased

Table V-2. Summary of Effects of Atrazine in Monogastric Animals Following Short-term Exposure

Reference	Species	Sex	Route	Daily dose (mg/kg)	Duration	Effect
IBT (1976)	Mouse	M/F	Oral (diet)	1.5-150	28 days	NOAEL
				450		Death in 2 of 10 animals
				1,500		Increased mortality; decreased body weight; tremors
				4,500		Increased mortality; decreased body weight; tremors
Molnar (1971)	Rat	NR[a]	Oral	600	Single dose	Death (6% in 6 hours, 25% of those remaining in 24 hours); damage to lungs, liver, kidneys
Santa Maria et al. (1986)	Rat	M	Oral	100-600	14 days	Increased electrolyte and protein excretion; decreased creatinine clearance
Castano et al. (1982)	Rat	NR	ip[b]	40 mg/rat twice wkly	30 days	Decrease in axonal areas of sciatic nerve fibers
Bashmurin (1974)	Cat	NR	Oral	100	Single dose	Hypotension
Bashmurin (1974)	Dog	NR	Oral	100	Single dose	Antidiuresis; decreased serum cholinesterase activity

[a]NR = Not reported.
[b]ip = Intraperitoneal.

Table V-3. Summary of Effects of Atrazine in Ruminants Following Short-term Exposure

Reference	Species	Sex	Route	Daily dose (mg/kg)	Duration	Effect
Palmer and Radeleff (1964)	Sheep, cattle	F	Oral	250	2 doses	Death
Palmer and Radeleff (1964)	Sheep	F	Oral	100	16 doses	Death
Palmer and Radeleff (1969)	Sheep	F	Oral (capsule)	5	10 days	Hindquarter spasms, stiff gait and stance; anorexia in both species
	Cattle	F	Oral (capsule)	25	10 days	Death
Geigy Chemical Corporation (1961)	Sheep	NR[a]	Oral (feed)	0.4-25 50 100 400	4-5 weeks 28 days 16 days 2 days	No deaths or pathology Body weight loss Death Death
Geigy Chemical Corporation (1961)	Cattle	F	Oral (feed)	0.045 0.23 1.5	21 days	No effect on food intake, milk production, or on overall physical condition
Johnson et al. (1972)	Sheep	F	Oral (feed)	40	25 days	For both species, no significant effects on body weight and no gross signs of adverse effects; clinical tests normal
	Cattle	NR	Oral (feed)	30	25 days	

[a] NR = Not reported.

incidence of cardiac thrombi was found in "early death" mice, whereas no statistically significnat increase in the incidence of cardiac thrombi was found in the group of mice who survived to terminal sacrifice in the same' exposrue group. No other dose-related effects were observed in mice in this group.

The LOAEL was set at 1,500 ppm and is based upon decreases of 23.5 and 11.0% in mean body weight gain in male and female mice, respectively, at 91 weeks. An increased incidence of cardiac thrombi found in female mice in the 1,500-ppm exposure group also influenced the selection of the LOAEL. None of the above effects were observed at 300 ppm; thus, the NOAEL was set at 300 ppm (corresponding to 38.4 and 47.9 mg/kg/day in males and females, respectively).

As reported by Nezefi (1971) (available in abstract form only), a number of pathological changes were observed in rats receiving atrazine orally for 6 months at a dosage of 20 mg/kg/day. No information was provided on the strain, sex, age, and number of rats used, or on the formulation and purity of the atrazine. Severe morphological alterations were noted in the central nervous system; parenchymal, endocrine, secretory, and sexual organs; and in physiological and biological functions. Forty percent of the rats died, usually with accompanying signs of respiratory distress and paralysis of the limbs. The results of this study are in contrast to those of Suschetet et al. (1974), who reported no toxicological effects of feeding comparable amounts of atrazine to rats.

Gzhetotskii et al. (1977) conducted a long-term study (specific duration not specified), in which atrazine was administered orally to rats at doses of 140 or 280 mg/kg. Adverse effects noted included reduced weight gain; hypercholesterolemia; reduced activity of peroxidase and carbonic anhydrase; reduced

hemoglobin levels, neutrophil, and monocyte counts; and increased lymphocyte counts.

Desi (1983) studied the neurotoxicological effects of atrazine in 10 adult male and female CFY rats fed technical atrazine (95% purity) in the diet over a 6-week period. Atrazine was fed at 1/20 or 1/40 of the previously determined LD_{50} (75 or 37.5 mg/kg/day, respectively). Behavioral studies and feeding were initiated simultaneously. Neither dose had any effect on the ability of atrazine-fed animals to run a maze.

Suschetet et al. (1974) fed Sprague-Dawley rats (16/sex/group) doses of 100 or 500 ppm atrazine in the diet for 183 days. Assuming an average body weight of 300 g and food consumption of 15 g/day (Arrington, 1972), these atrazine levels correspond to doses of 5 or 25 mg/kg/day. The high dose of atrazine caused reduced food intake and growth retardation in both the males and females (Table V-4). The authors were not able to determine whetner the diminished food intake was a manifestation of atrazine-induced toxicity or whether it was due to taste aversion. Accordingly, the significance of the changes in body weight and in the various other nutritional parameters studied is unclear. Various tissues were examined at the end of the study, but no histological lesions were observed in the atrazine-treated animals.

Hazleton Laboratories, Inc. (1961) fed atrazine to male and female rats for 2 years at dietary levels of 0, 1, 10, or 100 ppm, corresponding to doses of approximately 0, 0.05, 0.50, or 5.0 mg/kg/day. After 65 weeks, the 1.0-ppm dose was increased to 1,000 ppm (50 mg/kg/day) for the remainder of the study. No treatment-related pathology was found at 26 weeks, 52 weeks, or 2 years, or in animals that died and were necropsied during the study. Results of

blood and urine analyses were unremarkable. Atrazine had no effects on the general appearance or behavior of the rats. A transient roughness of the coat and piloerection were observed in some animals after 20 weeks of treatment at the 10- and 100-ppm levels but not at 52 weeks. Body weight gains, food consumption, and survival were similar in all groups for 18 months, but from 18 to 24 months there was high mortality due to infections (not attributed to atrazine) in all groups, including controls, which limits the usefulness of this study in determining a NOAEL for the chronic toxicity of atrazine.

A 2-year chronic feeding/oncogenicity study in Sprague-Dawley rats (Ciba-Geigy, 1986) was recently evaluated by EPA. In this study, technical atrazine (98.9% a.i.) was fed to 37- to 38-day-old Sprague-Dawley rats. The dose levels used were 0, 10, 70, 500, or 1,000 ppm, equivalent to 0, 0.5, 3.5, 25, or 50 mg/kg/day (using Lehman's conversion factor, 1959). Twenty rats/sex/group were used for the chronic toxicity group, i.e., rats used to measure blood parameters and clinical chemistries and urinalysis. Fifty rats/sex/group were used for the oncogenicity study and were maintained on diets for 24 months. An additional 10 rats/sex were placed on the control or high-dose diet (1,000 ppm) for a 12-month interim sacrifice, and another 10/sex were fed the control or 1,000-ppm diet for 13 months, but the ten animals in the 1,000-ppm group were placed on control diet for 1 month prior to sacrifice. The total number of animals/sex in this study was 90 in each of the control and high-dose groups, and 70 in the 10-, 70-, and 500-ppm groups. Histopathology was performed on all animals.

At the middle and high doses, a decrease was found in mean body weights of males and females (see Table V-4); and increased bone marrow myeloid hyperplasia in females. Survival was decreased in high-dose females but increased in high-dose males. Red cell parameters (hemoglobin, hematocrit, and red cell

Table V-4. Effects of Atrazine on Food Intake and Weight Gain in Male and Female Rats

Dose[a]	From days 6 to 27			From days 75 to 96			From days 162 to 183		
	Number of rats[b]	Weight gain (g)	Food intake (g)	Number of rats	Weight gain (g)	Food intake (g)	Number of rats	Weight gain (g)	Food intake (g)
Males									
Controls	16	6.4	15.4	16	2.1	19.5	16	0.7	19.7
100 ppm	16	5.9[c]	15.0	16	2.2	19.3	16	0.4	18.5
500 ppm	16	4.2[c]	12.4[c]	16	1.3[c]	15.8[c]	16	0.5	15.4[c]
Females									
Controls	16	3.5	12.3	16	0.9	14.3	15	0.8	16.0
100 ppm	16	3.6	12.5	16	1.1	14.7	15	0.3[d]	14.7
500 ppm	16	2.7[d]	10.8[c]	16	0.6[e]	12.4[c]	9	0	13.2[c]

[a]100 ppm = 5 mg/kg/day; 500 ppm = 25 mg/kg/day.
[b]Sprague-Dawley rats, 25 days of age at start of study.
[c]Significantly different from controls (Student's t-test), $p < 0.001$.
[d]$p < 0.05$.
[e]$p < 0.01$.

SOURCE: Adapted from Suschetet et al. (1974).

count) were decreased in high-dose females, but not in males. The serum glucose level was decreased in high-dose females at 3, 6, and 12 months, and serum triglyceride levels tended to be decreased in high-dose males throughout the study; however, the toxicologic importance of the clinical chemistry findings is unclear. There were decreases in organ-to-body weight ratios in high-dose animals, which were probably the result of body weight decreases. Hyperplastic changes in high-dose males (mammary gland, bladder, and prostate) and females (myeloid tissue of bone marrow and transitional epithelium of the kidney) were of questionable toxicologic importance. There was an increase in retinal degeneration and in centrilobular necrosis of the liver in high-dose females and an increase in degeneration of the rectus femoris muscle in high-dose males and females when compared to controls. Based on decreased body weight gain, the LOAEL for nononcogenic activities in both sexes is 25 mg/kg/day and the NOAEL is 3.5 mg/kg/day. However, oncogenic activities were noted at 3.5 mg/kg/day (70 ppm) and above, as reflected in the increased incidence of mammary gland tumors in females (details in Section V.E, Carcinogenicity).

In a study by Woodard Research Corporation (1964), atrazine (80W formulation) was fed to groups of four male and four female beagle dogs for 105 weeks at levels of 0, 15, 150, or 1,500 ppm (0, 0.35, 3.5, or 35 mg/kg/day, respectively). Survival rates, body weight gain, food intake, behavior, appearance, hematology, urinalysis, organ weights, and histology were determined. The 15-ppm dose produced no toxicity, but the 150-ppm dose caused a decrease in food intake as well as increased heart and liver weights in females. In the group receiving 1,500 ppm atrazine, there were decreases in food intake and body weight gain, an increase in adrenal weight, a decrease in hematocrit, and occasional tremors or stiffness in the rear limbs. There were no changes in the histology of the 30 tissues examined. Based on changes in organ weights at

150 ppm, the NOAEL for chronic atrazine toxicity from this study can be identified as 15 ppm (0.35 mg/kg/day).

EPA recently evaluated a study conducted by Ciba-Geigy (1987b) in which technical-grade atrazine (97% a.i.) was fed to 5-month-old beagle dogs for 52 weeks. Following a 1-month laboratory acclimation period, the dogs were assigned randomly to one of four groups: 0, 15, 150, or 1,000 ppm. The atrazine-fortified diets corresponded to actual average intakes of 0.48, 4.97, or 33.65/33.8 (male/female) mg/kg/day. Six animals/sex/group were assigned to the control and high-dose groups and four animals/sex/group were assigned to the low- and mid-dose groups. One mid-dose male, one high-dose male, and one high-dose female had to be sacrificed moribund during the study period. It is not clear if the deaths of the mid-dose and high-dose males were compound-related; the testing laboratory indicated that only the death of the high-dose female was compound-related, and the deaths in the two males, especially the mid-dose male, appeared to be related to spontaneous dog pathology rather than to treatment. However, it cannot be ruled out that these deaths may also be compound-related. Decreased body weight gains and food consumption were noted at the high-dose level. Statistically significant ($p < 0.05$) reductions in erythroid parameters (red cell count, hemoglobin, and hematocrit) in high-dose males were noted throughout the study as well as mild increases in platelet counts in both sexes. Slight decreases in total protein and albumin ($p < 0.05$) were noted in high-dose males as well as decreased calcium and chloride in males and increased sodium and glucose in females. Decreased absolute heart weight and increased relative liver weight were noted in high-dose females and males, respectively. The mid-dose females inhibited an increase in absolute heart weight and heart/brain weight ratios.

The most significant effect of atrazine in this study (Ciba-Geigy, 1987b) was the cardiopathy syndrome noted in the high-dose animals of both sexes. This syndrome was reflected in discrete myocardial degeneration. Clinical signs associated with cardiac pathology such as ascites, cachexia, labored/shallow breathing, and abnormal EKG were observed in the group as early as 17 weeks into the study. Gross pathology reflected severe dilation of the right atrium and occasionally of the left atrium. These findings were also noted histopathologically as degenerative atrial myocardium (atrophy and myolysis). In the mid-dose group, two males appeared to be affected; one gross necropsy in one male revealed a moderate degree of dilation of the right atrium and minimal dilation of the left atrium, plus a pale lesion of epicardium of the left ventricle. However, no histopathological findings were noted. In the second mid-dose male, red right atrium "thickened with edema" was considered by laboratory investigators to be a spontaneous occurrence in the beagle dog, although the finding is consistent with "polyarteritis nodosa;" this animal's death occurred before the end of the study and was considered by the testing laboratory to be unrelated to compound administration. The mid-dose females in this study also exhibited a decrease in P-II waves at day 175 of the study; these P-II levels were within the normal range, but they reflect a trend toward the development of cardiac pathology that was noted at the higher dose. This study suggested a LOAEL and a NOAEL of 5 mg/kg/day, and 0.5 mg/kg/day, respectively.

In oder to help the agency to determine the relationship between potentially life-threateniny lesions seen at the high dose and effects of much lower magnitude and less frequency seen at the mid-dose, EPA requested the registrant (Ciba-Geigy) to carry out an additonal subchronic study in dogs (Copley, 1989). The registrant presented detailed analysis of the cardiac data and requested the EPA to reconsider the need for additional subchronic study.

Table V-5. Summary of Long-Term Exposure Toxicity of Atrazine

Reference	Species	Sex	Route	Daily dose (mg/kg)	Duration	Effect
Ciba-Geigy (1987c)	Mouse	M/F	Oral (feed)	38.4	91 weeks	NOAEL
				194 386		LOAEL Cardiac thrombi in females; decreased mean body weight and decreased erythrocyte count, hematocrit, and hemoglobin in both sexes
Suschetet et al. (1974)	Rat	M/F	Oral (feed)	5 25	183 days	Reduced food intake, reduced body weight; no histological lesions (both doses)
Nezefi (1971)	Rat	NR	Oral	20	6 months	Morphological changes in central nervous system, parenchymal, endocrine, secretory, and sexual organs; alterations of physiological and biological functions; death of 40% of animals, with respiratory distress and paralysis of limbs
Gznegotskii et al. (1977)	Rat	NR[a]	Oral	140 280	Long-term	Hypercholesterolemia, reduced hemoglobin, altered serum enzymes, impaired growth
Ciba-Geigy (1986)	Rat	M/F	Oral	3.5	104 weeks	No nononcogenic chronic effects; however, dose-related increase in mammary gland tumors in females were observed at this level and above
				25		LOAEL Decreased body weight gain in both sexes; and bone marrow-increased myeloid hyperplasia in females

Table V-5. (continued)

Reference	Species	Sex	Route	Daily dose (mg/kg)	Duration	Effect
Ciba-Geigy (1986) (Con't)	Rat	M/F	Oral	50	104 weeks	Decreased body weight gain, decreased organ-to-body weight ratios, and increased muscle degeneration in males and females; decreases in survival, hemoglobin, hematocrit, red cell count, and serum, glucose levels, increases in retina degeneration and liver necrosis, and hyperplasic changes in myeloid tissue of bone marrow and in transitional epithelium of the kidney in females; decreased serum triglyceride levels and hyperplastic changes in mammary gland, bladder, and prostate tissue in males
Woodard Research Corp. (1964)	Dog	M/F	Oral	0.35	105 weeks	NOAEL
				3.5		Decreased food intake; increased organ weights
				35		Decreased food intake, reduced body weight; tremors, stiffness in hind limbs; increased adrenal weight
Ciba-Geigy/ Copley (1987b,1989)	Dog	M/F	Oral (feed)	5 34	52 weeks	NOAEL LOAEL Statistically significant decreased P-II waves, and cardiac toxicity

Table V-5. (continued)

Reference	Species	Sex	Route	Daily dose (mg/kg)	Duration	Effect
Ciba-Geigy/ Copley, (1987b,1989)	Dog	M/F	Oral (feed)	5 34		NOAEL LOAEL Increased heart rate, decreased P-II va ues, atrial premature om-plexes, atrial filibra-tion, and moderate to severe cardiac lesions (dilation of the right atrium, atrophy, and myolysis)
Binns and Jonnson (1970)	Sheep	F	Oral (feed)	15	180 days	None
Palmer and Radeleff (1964)	Sheep	F	Oral (capsule)	50	199 days	Spasms, stiff gait, increased respiration

[a] NR = Not reported.

The original LOAEL was based on decreased amplitude of P II wave at only 1 time period in females, atrial dialation and one case of poly arteritis nodosa. At the high dose, the first two effects occurred at a much higher freguency and magnitude and were accompanied by severe histophatologic cardiac lesions. Detailed analysis of the individual animal data indicated that the effects observed at the mid-dose were not likely to be atrazine-related. The apparent significnat decrease in P-II amplitude of only 0.1 mV was observed in only 1 mid-dose female at only one time point (day 171). Corresponding, histopathological lesions were not observed at this dose level. The amplitude change was very small which could readily occur due to slight positional change during EKG process. Changes of 0.1 mV were present in other groups including controls at other time points. Polyarteritis lesion that occurred in 1 male dog was evaluated and found to be not of the type produced by chemical toxictiy. Atrial dilation seen only at necropsy in the males could not be attributed as treatment-related due to lack of supporting pathology data.

Based on the supplemental data, the agency has changed the NOAEL for the chronic dog study from 0.5 mg to 5.0 mg/kg/day. The LOAEL has been changed from 5 mg to 34 mg/kg/day based on death, cachexia, ascities, decreased body weight and body weight gain, decreased food consumption, EKG changes and cardiac leisons.

No toxic effects were observed after atrazine was administered in feed for 180 days to one female sheep (15 mg/kg/day) (Binns and Johnson, 1970). In a study by Palmer and Radeleff (1964), one female sheep was given a daily dose of 50 mg/kg atrazine (in capsule form). No toxic effects were observed until 199 days had elapsed, at which time muscular spasms and fasciculation, stiff gait, and increased respiratory rate were observed.

C. REPRODUCTIVE/TERATOGENIC EFFECTS

A study carried out by Bionetics Research Laboratories (1968), under contract from the National Cancer Institute, examined the teratogenicity of a number of pesticides and herbicides in mice. Atrazine was administered at a daily subcutaneous dose of 46.4 mg/kg in 0.1 mL DMSO to females on days 6 to 14 or 15 of gestation. Mice were sacrificed on day 18 or 19 of gestation, fetuses were examined for anomalies, and the numbers of resorption sites and dead fetuses were scored. Fetal mortality was increased in C3H- and AKR-strain mice, but decreased in C57 mice. The incidences of abnormal fetuses were in the normal ranges in all groups. The use of DMSO in this study and insufficient data on litters make evaluation of this study difficult.

A three-generation study of the effects of dietary ingestion of atrazine on reproduction in rats was conducted by Woodard Research Corp. (1966). Groups of 10 males and 20 females received 0, 50, or 100 ppm atrazine in their food. Based on a conversion factor of 1 ppm to 0.05 mg/kg/day, these concentrations corresponded to approximately 0, 2.5, and 5 mg/kg/day, respectively. The animals initially received only half of these concentrations and were changed to the stated levels after 3 weeks. After 74 days of dosing at the stated levels, rats within each group were paired for mating over a 10-day period. Following birth of the litters, pups were weighed and examined and the number of births and stillbirths recorded. At weaning, the pups were weighed and examined, and the number of survivors and the mean litter weights were recorded. The pups were then sacrificed and necropsied. Approximately 13 days after the first weaning, the females in each group were remated with different males in the same group. The protocol employed following the first mating was repeated with the pups from the second mating. After the second weaning, the

parents (F_0 generation) were sacrificed, and the weanlings (F_{1b} generation) were used to form another three groups.

The entire series of tests was repeated following the dosing of the F_{1b} generation with 0, 50, or 100 ppm (0, 2.5, or 5 mg/kg/day, respectively) atrazine for 105 days prior to breeding and thereafter. The F_{2b} generation was, in turn, fed atrazine for 75 days prior to breeding and thereafter. The entire protocol was repeated until the weaning of the F_{3b} generation; at this point, the study was terminated. No adverse affects of atrazine on reproduction were observed during the course of the three-generation study. Atrazine had no effect on any of the following parameters: mean parental body weight, survival, appearance, benavior, number of litters/group, number of live births, mean pup weights at birth and weaning, and pup survival at weaning. In addition, there were no histologic changes noted in the weanlings and no atrazine-related effects on fetal resorption. No malformations were observed in the atrazine-treated groups, and weanling organ weights were similar in F_{3b} controls and atrazine-treated animals. A NOAEL of 100 ppm (5 mg/kg/day) was identified for this study. However, the evaluation of this study is difficult because only two relatively low dosages, which were without observable toxicity, were used. In addition, the dietary concentrations of atrazine were altered during an important maturation period of the neonates (F_0 parental generation).

A two-generation study in rats by Ciba-Geigy (1987a) was conducted using 97% a.i. technical atrazine. Young rats, 47 to 48 days old, were maintained on the control and test diets for 10 weeks before mating. The concentrations used were 0, 10, 50, and 500 ppm (equivalent to 0, 0.5, 2.5, and 25 mg/kg/day using the Lehman conversion factor, 1959). Thirty animals/sex/group were used in each generation; one litter was produced per generation. The levels tested had no

effect on mortality in either generation. Body weight and body weight gains were significantly depressed ($p < 0.05$) at the highest dose; food consumption was also decreased at the high-dose level in parental males and females during the premating period and for the first generation females (F_1) on days 0 to 7 of gestation. No histopathological or other effects were noted during gross necropsy in either parental generation with the exception of increased testes-to-body weight in both generations at the high dose. In pups of both generations, a significant reduction ($p < 0.05$) in body weight was noted; however, this effect was dose-related only in the second generation (F_2) at both the mid- and high-dose levels on postnatal day 21. The maternal toxicity NOAEL is 2.5 mg/kg/day, and the LOAEL is 25 mg/kg/day based on decreased body weights, body weight gain and food consumption in both parental males and females throughout the study. The reproductive NOAEL is 0.5 mg/kg/day, and the LOAEL is 2.5 mg/kg/day based on reduced pup weight in the second generation at the time of weaning (postnatal day 21).

Atrazine was administered orally by gavage to pregnant rats on gestation days 6 to 15 at dose levels of 0, 100, 500, or 1,000 mg/kg (Ciba-Geigy Ltd., 1971). The two higher doses increased the number of prenatal deaths, decreased the mean weights of the fetuses, and retarded skeletal development. Anasarca was noted in 5/119 fetuses only at the 1,000-mg/kg dose. The highest dose (1,000 mg/kg) resulted in 23% maternal mortality and various toxic effects. The 100-mg/kg dose was the NOAEL for this study; there were no effects on either dams or embryos.

In a subsequent study (Ciba-Geigy, 1984a), Charles River rats (27 per dose level) received atrazine of 96.7% purity by gavage on gestation days 6 through 15 at dose levels of 0, 10, 70, or 700 mg/kg/day. Excessive maternal mortality (21/27) was noted at 700 mg/kg/day, and reduced weight gains and food consump-

tion were noted at both 70 and 700 mg/kg/day. Developmental toxicity was also present at these dose levels. Fetal weights were severely reduced at 700 mg/kg/day, and delays in skeletal development occurred at 70 mg/kg/day. This study with rats esta lished a NOAEL of 10 mg/kg and LOAEL of 70 mg/kg for maternal toxicity, based on a statistically significant decrease in body weight gain during the final half of the dosing period and a statistically significant reduction in food consumption for the first 2 days of agent administration. Additionally, at 700 mg/kg/day there was increased mortality and clinical signs of toxicity as well as decreased food consumption. The NOAEL and LOAEL for developmental toxicity is established at 10 mg/kg aand 70 mg/kg, respectively. The LOAEL is based on delayed ossification of appendages (U.S. EPA, 1989).

New Zealand White rabbits (19 per dose level) received atrazine of 96.3% purity by gavage on gestation days 7 through 19 at dose levels of 0, 1, 5, or 75 mg/kg/day (Ciba-Geigy Corp., 1984b). Maternal toxicity, evidenced by decreased body weight gains and food consumption, was present in the mid- and high-dose groups. Developmental toxicity was demonstrated only at 75 mg/kg/day by an increased resorption rate, reduced fetal weights, and delays in ossification. No teratogenic effects were indicated. The NOAEL for developmental toxicity was 5 mg/kg, with a LOAEL of 75 mg/kg based on a statistically significant increase in the number of resorptions, significantly decreased fetal weights (male and female), and an increase in skeletal variations, especially delayed ossification of appendicular skeletal elements at this dose level. Based on a statistically significant reduction in body weight gain for gestational days 14 to 19 and a statistically significant reduction in food consumption on gestational days 17 and 19, this study established a NOAEL of 1 mg/kg and a LOAEL of 5 mg/kg for maternal toxicity.

Peters and Cook (1973) fed atrazine to pregnant rats (four rats per group) at levels of 0, 50, 100, 200, 300, 400, 500, or 1,000 ppm in the diet throughout gestation. Assuming a body weight of 300 g and a daily food consumption of 12 g (Arrington, 1972), these levels correspond to approximately 0, 2, 4, 8, 12, 16, 20, or 40 mg/kg/day, respectively. The number of pups per litter was similar in all groups, and there were no differences in weanling weights. This study identified a NOAEL of 40 mg/kg/day for developmental effects. In another study, Peters and Cook (1973) demonstrated that subcutaneous injections of 50, 100, or 200 mg/kg atrazine in DMSO on gestation days 3, 6, and 9 had no effect on litter size, while a dose of 800, 1,000, or 2,000 mg/kg was embryolethal. Therefore, a NOAEL of 200 mg/kg by the subcutaneous route was identified for embryotoxicity.

Binns and Johnson (1970) administered daily doses of atrazine (15 or 30 mg/kg, mixed in alfalfa meal, by gastric intubation) to pregnant ewes throughout gestation and for 30 days postpartum. The group of six ewes fed 30 mg/kg/day all died between days 36 and 60 of gestation. Within this group, one ewe failed to conceive, three had embryonic deaths, and two were carrying apparently normal fetuses. In the group of six ewes fed 15 mg/kg/day, all lambs were born at full term and were normal. The lambs then nursed for 30 days without adverse effects. The dose of 15 mg/kg/day was considered the highest level expected to be ingested from atrazine-treated plants.

A summary of these studies on the reproductive effects of atrazine is presented in Table V-6.

Table V-6. Summary of Reproductive and Developmental Effects of Atrazine

Reference	Species	Route	Duration	Dose (mg/kg/day)	Result
Woodard Research Corp. (1966)	Rat	Oral	Three generations	5	NOAEL
Ciba-Geigy (1987a)	Rat	Oral (feed)	Two generations	0.5	NOAEL for reproductive effects
				2.5	LOAEL for reproductive effects based on reduced pup weight (F_2 generation, postnatal day 21).
				2.5	NOAEL for maternal toxicity.
				25	LOAEL for maternal toxicity based on decreased body weight, body weight gain and food consumption in both sexes.
Ciba-Geigy Ltd. (1971)	Rat	Oral	Gestation days 6 to 15	100	NOAEL
				500	Increased prenatal mortality
				1,000	Maternal mortality (23%); fetal anarsarca
Ciba-Geigy (1984a)	Rat	Oral	Gestation days 6 to 15	10	NOAEL for maternal toxicity and LOAEL for developmental effects; dose-related increase in runts.
				70	Maternal toxicity; delayed fetal skeletal development

Table V-6. Summary of Reproductive and Developmental Effects of Atrazine (Continued)

Reference	Species	Route	Duration	Dose (mg/kg/day)	Result
				700	Maternal mortality (78%); severely reduced fetal weights
Peters and Cook (1973)	Rat	Oral (feed)	Gestation	40	NOAEL for developmental effects
Ciba-Geigy (1984b)	Rabbit	Oral	Gestation days 7 to 19	1	NOAEL for maternal toxicity
				5	Maternal toxicity
				75	Increased resorption rate and reduced pup weight
Binns and Jonnson (1970)	Sheep	Oral (stomach tube)	Gestation and 30 days postpartum	15	NOAEL
				30	Maternal mortality (100%)
Bionetics Research Laboratories (1968)	Mouse	Subcutaneous (in DMSO)	Gestation days 6 to 14 or 15	46.4	NOAEL
Peters and Cook (1973)	Rat	Subcutaneous (in DMSO)	Gestation days 3, 6, and 9	200	NOAEL for embriotoxicit
				800	Embryo letnality

D. MUTAGENICITY

The genotoxic potential of atrazine was evaluated in a series of studies sponsored by the European Economic Community. Results for many of the investigations were presented as abstracts, and the overall summarized findings (Table V-7) were published by Adler (1980). Since few of the assays have appeared as full publications, the information needed to critically evaluate the findings is not available. The majority of these studies, therefore, serve only as supportive information. This review focuses on studies with sufficient primary data to permit an independent assessment of results and conclusions; also included are the results of two recent assessments of atrazine genotoxicity.

In vitro and *in vivo* genetic toxicology assays on atrazine are categorized into gene mutation (category 1), chromosome aberration (category 2), and other mutagenic mechanisms (category 3). The findings are discussed below and summarized in Table V-8.

1. Gene Mutation Assays (Category 1)

a. Gene mutation in prokaryotes

Three unpublished studies evaluated atrazine in the *Salmonella typhimurium* mammalian/microsome reverse mutation assay (Ames test). Simmon et al. (1977) exposed *S. typhimurium* TA1535, TA1537, TA1538, TA98, and TA100 to six doses of atrazine (5 to 5,000 ug/plate) in both the absence and presence of a 10% Aroclor 1254-induced rat liver S9 mix. Arni and Muller (1978) used the same tester strains to evaluate an atrazine dose range of 10 to 810 ug/0.1 mL; the S9 mix in this study contained 30% liver homogenate. Utilizing a similar protocol, Sutou et al. (1979) performed Ames tests on seven nonactivated and S9-activated

Table V-7. Summary of Studies on the Mutagenicity of Atrazine

Genetic endpoint	Organism	Marker	In vitro			In vivo	
			Microsome source	Atrazine concentration (mM)	Result	Dose (mg/kg)	Result
Reversion	S. typhimurium	his+	plant		neg	1,000	neg
Forward mutations	E. coli	Amp^R		0.5-2	neg	100-600	pos
	S. typhimurium	$8AG^R$		0.2-1.1	neg		
	A. nidulans	$8AG^R$	potato		pos		
	S. pombe	5 loci	potato	6	pos	1,000	pos
	S. coelicolor	$Strp^R$	potato		pos		
	V79 cells	$6TG^R$	liver	1.2-10	neg		
Mitotic gene conversion	S. cerevisiae	trp5-12/27	potato	2.5-10	neg		
Mitotic crossing cover	A. nidulans	fpa A1	potato		pos		
Recessive lethals	Drosophila					5-10	neg
Chromosome breakage	CHO cells			1.2-10	neg		
	Mouse bone marrow					2,000	pos
Dominant lethals	Mouse spermatids					1,500-2,000	pos

[a] Sponsored by the European Economic Community.

SOURCE: Adapted from Adler (1980).

Table V-8. Genotoxicity of Atrazine

Reference	Genetic endpoint	Organism	Dose range	Response	Comments
Simmon et al. (1977)	Reverse-gene mutation	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	5-5,000 ug/plate; +/- 10% Rat S9	-	Minor technical flaws; acceptable
Arni and Muller (1978)	Reverse-gene mutation	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	10-810 ug/0.1 mL; +/- 30% Rat S9	-	Minor technical flaws, acceptable
Sutou et al. (1979)	Reverse-gene mutation	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	50-10,000 ug/plate; +/- 30% Rat S9	-	Minor technical flaws; acceptable
Plewa et al. (1984)	Reverse-gene mutation	S. typhimurium TA98	Extract from corn exposed to 1.66 x 10-5 M metolachlor/1.37 x 10^{-4} M atrazine + corn 1S fraction	+	Inconclusive single dose; weak response; technically deficient
Sutou et al. (1979)	Reverse-gene mutation	E. coli WP_2 hcr-	50-5,000 ug/plate; +/- 30% Rat S9	-	Acceptable
Singh et al. (1982)	Gene conversion	S. cerevisiae D4	Water-soluble extracts of maize exposed to 30, 60, 90 ppm A Atrex	+	Inconclusive; no dose response
	Gene conversion	S. cerevisiae D4	Methanol extracts of above	+	Acceptable; dose related
Plewa and Gentile (1976)	Gene conversion	S. cerevisiae D4	Extracts of maize exposed to 15, 20, 25 ppm	+	Acceptable; dose related

Table V-8. (continued)

Reference	Genetic endpoint	Organism	Dose range	Response	Comments
Benigni et al. (1979)	Gene mutation and somatic segregation	*A. nidulans*	Unreported dose and plant metabolic activation	+	Supportive result; insufficient data
Plewa et al. (1984)	Gene mutation	*Z. mays*	*In situ* treatment of corn with atrazine or atrazine formulated with metolachlor or eradicane	+	Acceptable; results confirmed
Simmon et al. (1977)	*In vivo* Gene mutation (host-mediated assay)	Mouse (male)/ *S. typhimurium* TA1535 and TA1538	Acute oral administration 6 doses (500-2,200 mg/kg)	-	Acceptable; assayed to a cytotoxic level
			Subacute oral administration 3 doses (275 to 1,100 mg/kg x 5 days)	-	Acceptable; assayed to a cytotoxic level
Solt and Neale (1980)	*In vivo* Gene mutation (host-mediated assay)	Mouse/*E. coli*	Oral administration 100-600 mg/kg	+	Supportive result; abstract
Murnik and Nash (1977)	Sex-linked recessive lethal mutations	*D. melanogaster*	Larval feeding 0.01%	+	Acceptable
			0.012% administered by injection to adults	-	Unacceptable; insufficient sample size
Hook et al. (1981)	Chromosome aberrations (somatic cells)	Chinese hamsters (males and females)	Oral administration 282, 564, 1,128 mg/kg	-	Inconclusive; entire cell cycle not assayed

Table V-8. (continued)

Reference	Genetic endpoint	Organism	Dose range	Response	Comments
Loprieno et al. (1980)	Chromosome aberrations (somatic cells)	Mouse	Route not reported 1 and 2 g/kg	+	Supportive result; abstract
Chollet et al. (1982)	Chromosome aberrations (somatic cells)	Mouse	ip administration; 6 mg/kg	-	Supportive result; abstract
Chollet et al. (1982)	Chromosome aberrations (germinal cells): dominant lethal assay; germinal cell metaphases	Mouse	ip administration; 6 mg/kg	-	Supportive result; abstract
Hool and Muller (1981)	Chromosome aberrations (germinal cells): dominant letnal assay	Mouse	Gavage administration; 444 and 1,332 mg/kg	-	Unacceptable; maximum tolerated dose not assayed
Usterlon et al. (1983)	Sperm morphology assay	Mouse	ip administration; 600, 1,200, 2,400 mg/kg/day for 5 days	-	Acceptable; assayed to a toxic level
Sutou et al. (1979)	DNA damage/ repair	B. subtilis M45 and H17	100-10,000 ug/ well - S9	-	Acceptable - S9; study is incomplete
Ghiazza et al. (1984)	Sister chromatid exchange	Human lymphocytes	0.001, 0.01, and 0.1 ppm	-	Unacceptable; no cytotoxic dose

doses of atrazine (50 to 10,000 ug/mL). These studies were individually flawed by technical deficiencies. Collectively, however, the results indicated that an atrazine concentration range of 10 to 5,000 ug/plate, either nonactivated or in the presence of low (10%) or high (30%) Aroclor 1254-induced rat liver S9, was not mutagenic in S. typhimurium TA1535, TA1538, TA98, and TA100. Sutou et al. also found atrazine (50 to 5,000 ug/plate) to be nonmutagenic with or without S9 activation in an acceptable reverse mutation Escherichia coli WP2 ncr assay. Results from in vitro bacterial assays summarized by Adler (1980) confirmed the absence of mutagenicity.

b. Lower eukaryotes

Singh et al. (1982) exposed maize kernels to 0, 30, 60, and 90 ppm A Atrex (80% atrazine) and allowed them to germinate; plants were harvested and extracts prepared. The extracts caused increased gene conversion in Saccharomyces cerevisiae at the adenine (ade 2) and tryptophan (trp 5) loci; however, the effect was not pronounced. The dose causing the greatest response (60 ppm) yielded 2.7- and 2.2-fold increases in conversion frequencies at the ade 2 and trp 5 loci, respectively. The authors demonstrated clear dose-related responses at both loci when a methanol extract of atrazine was tested in the same protocol. The 30, 60, and 90 ppm methanol extracts increased gene conversion 2.4-, 2.5-, and 3.4-fold at the ade 2 locus and 1.7-, 2.4-, and 4.2-fold at the trp 5 locus.

Plewa and Gentile (1976) provided similar evidence showing that extracts of maize exposed to 15, 20, and 25 ppm atrazine induced gene conversion at the ade 2 and trp 5 loci in S. cerevisiae D4. Using a different plant metabolic activation system (Nicotiana alata) and a higher eukaryote, Benigni et al. (1970) demonstrated a marked increase in mutation and somatic segregation fol-

lowing exposure of Aspergillus nidulans to an unreported concentration of atrazine. In the presence of mammalian in vitro metabolism, Adler (1980) reported that atrazine was not mutagenic in yeast or fungi; however, in the presence of potato microsomes, mutagenic activity was observed in A. nidulans and two yeast species. The commercial grade of atrazine or atrazine combined with metolachlor or eradicane, assayed in situ with emerging maize seedlings, induced mutations at the wx locus in Zea mays (Plewa et al., 1984). The same authors presented data indicating that in vitro plant-activated extracts from corn treated with 1.66 x 10-5 M metolachlor/1.37 x 10-4 M atrazine was mutagenic in S. typhimurium TA98. The study was compromised by the unusually high negative control value and the weak effect (2.3-fold increase) at the highest reactive dose; the results are, therefore, considered inconclusive.

c. In vivo gene mutations

1) Host-mediated assay

The acute (six doses ranging from 500 to 2,200 mg/kg) or subacute (five consecutive daily doses of 275 to 1,100 mg/kg) oral administration of atrazine to male mice induced a cytotoxic but not mutagenic response in S. typhimurium TA1535 or TA1538 (Simmon et al., 1977). This well-controlled study assayed atrazine to a level demonstrating cytotoxic interaction with the target cell but no mutagenicity. By contrast, atrazine (100 to 600 mg/kg) administered orally to mice induced a mutagenic response in E. coli (increase in ampicillin-resistant mutants). Although the results of this study were initially presented as an abstract by Solt and Neale (1980) and subsequently published by Adler (1980), neither author indicated that the effect was dose-dependent or confirmed. Also reported by Adler were negative results for a series of S. typhimurium/mouse host-mediated assays with 1,000 mg/kg atrazine.

2) Sex-linked recessive lethal mutations in Drosophila melanogaster

Murnik and Nash (1977) presented data showing a significant ($p < 0.05$) increase in the rate of lethal mutations in Drosophila melanogaster after feeding 0.01% atrazine to the larvae. Since the authors reported that atrazine was fed throughout the larval stage, it can be assumed that the offspring scored for mutations represent germ cells in the early stages of spermatogenesis. The same authors found that 0.012% atrazine, administered by injection to adult males, did not increase lethal mutations in germ cells sampled at intervals timed to correspond with different stages of spermatogenesis. However, the number of chromosomes examined from later broods, arising from spermatids and spermatogonia at treatment, was too small to provide confidence in the results. Adler (1980) listed atrazine (5 to 10 mg/kg) as negative in this system. The available data are insufficient to refute the larval feeding study results; however, the relevance of the finding is uncertain at this time.

c. Overall conclusions for gene mutations

Atrazine does not appear to induce gene mutations in the presence or absence of exogenous metabolic activation derived from mammals. However, plant microsomes can convert atrazine to a reactive form that is mutagenic in bacteria, yeast, and fungi. This conclusion is consistent with the assessment of Dearfield (1988) that atrazine is a plant-activated promutagen.

2. Chromosome Aberration Assays (Category 2)

a. Somatic cells

No acceptable in vitro chromosome aberration studies were found. Adler (1980) reported that an oral dose of 2,000 mg/kg induced a significant increase

in the frequency of chromatid breaks in mouse bone marrow cells. Loprieno et al. (1980) found similar evidence that 1 and 2 g atrazine/kg elicited clastogenic responses in mouse bone marrow cells; no further information was furnished.

By contrast, Chollet et al. (1982) reported that the ip administration of 6 mg/kg atrazine did not increase the incidence of chromosome aberrations in mouse bone marrow metaphases sampled over the entire cell cycle; the results, presented in an abstract, were not detailed. Atrazine did not increase the frequency of micronucleus induction in male or female Chinese hamsters administered oral doses equivalent to 282, 564, or 1,128 mg/kg (Hook et al., 1981). The sensitivity of this assay to detect clastogenic activity at different stages in the cell cycle is, however, questionable. Brusick (1987) reported that the results of a mouse micronucleus assay performed with atrazine administered at 2,000 mg/kg by oral gavage were negative; however, no further details were provided.

b. Germinal cells

Adler (1980) reported that atrazine (1,500 and 2,000 mg/kg) induced dominant lethal mutations in mouse spermatids; no further details were provided.

An increase in preimplantation loss, 4 weeks after treatment of male mice with 6 mg/kg atrazine, was observed and reported in the abstract of Chollet et al. (1982). The more critical index of dominant lethality, postimplantation loss, was not increased. At the same dose level, no adverse effects were noted in spermatogonia and spermatocyte metaphases collected from mice treated acutely or subchronically. In a mouse dominant lethal assay, a dose of 6 mg/kg atrazine administered ip (444 or 1,332 mg/kg by gavage), was not clastogenic (Hool and Muller, 1981); however, a maximum tolerated dose was not achieved. Although not specifically a measurement of clastogenicity, the mouse-sperm

morphology assay of Osterlon et al. (1983) demonstrated that atrazine has no genotoxic effect on spermatogenesis. This assay provided clear evidence of toxicity (no animals survived five consecutive daily ip injections of 1,200 or 2,400 mg/kg/day, but no testicular cytotoxic or genotoxic effects were observed in animals dosed with 600 mg/kg/day, all of which survived.

c. Conclusions for chromosome aberrations:

No definitive conclusions can be reached regarding the potential of atrazine to induce clastogenic effects in somatic or germinal cells. Although the majority of the studies were negative, they do not offset the positive results for two reasons: (1) the Office of Pesticide Programs (OPP), Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency (Dearfield, 1988) considers many of these *in vivo* studies to be scientifically unacceptable; and (2) the negative *in vivo* studies either assayed low doses of atrazine or evaluated doses equivalent to those showing a positive response, but used less sensitive endpoints (i.e., micronucleus assay).

3. Other Mutagenic Mechanisms (Category 3)

a. DNA damage/repair in bacteria

Six concentrations of atrazine (ranging from 100 to 10,000 ug/well) did not cause preferential inhibition of repair-deficient *B. subtilis* M45 without activation when compared to the parental and repair-competent H17 strain (Sutou et al., 1979). The concentrations evaluated in this assay are considered acceptable levels in the absence of a positive response; however, the lack of exogeneous metabolic activation renders the study incomplete.

b. Sister chromatid exchange (SCE)

Ghiazza et al. (1984) exposed human lymphocytes to three noncytotoxic doses of atrazine (0.001, 0.01, and 0.1 ppm); no significant increase in SCE was noted. Since the highest level tested was not cytotoxic, the assay is not fully acceptable.

c. Unscheduled DNA synthesis (UDS)

The unpublished UDS primary rat hepatocyte and human fibroblast assays performed by Puri and Muller (1984a,b) were compromised by major technical deficiencies and, hence, provide no meaningful data.

4. Recent Assessments of Atrazine Genotoxicity

Ciba-Geigy (1988) indicated that the weight-of-evidence approach should be used in the assessment of atrazine mutagenicity as it was already performed by Brusick (1987). An excellent summary of the available mutagenicity studies on atrazine were discussed in this document by Brusick for Ciba-Geigy. Brusick concluded that:

> "It is not scientifically possible, nor totally necessary, to reconcile all the test-response conflicts for atrazine. In some cases, such as the Drosophila SLRL assays, it is relatively easy to dismiss the studies in which sample sizes varied and nonconcurrent negative controls were used. In other cases, such as the mouse dominant lethal studies, it appears that two studies using approximately equivalent gavage dose levels produced different responses. The evidence for bone marrow aberrations is considered very weak due to several negative studies including two micronucleus assays at equal doses.
>
> By using a quantitative weight-of-evidence system developed by ICPEMC all test data including positive and negative studies could be evaluated for a consensus trend. The results of using this approach indicated that the consensus score for atrazine ranged from approximately 16 to 20, suggesting that the positive responses were outliers and might be due to technical deficiencies or improper study designs. The weight-of-evidence analysis places atrazine in a nonmutagenic status, in my opinion, relative to conventional health effects testing formats.

The issue of plant activation is not easily interpreted. However, a strong position can be taken that extrapolation of genotoxic activity for the plant activation studies to effects in mammals or mamalian cells has not been documented. Without such documentation one can only define a risk to plant somatic and germ cells from atrazine exposure. Studies in which plant-activated intermediates or extracts froms treated plants produced clear evidence of mutation in mammalian cells (in vitro or in vivo) will be required for this extrapolation. The positive results alledged by Loprieno et al. (1980) for gene mutation and UDS in mammalian cells exposed to atrazine and potato microsomes are not sufficient without suitable documentation and confirmation.

Consequently, I do not believe that an adequate case has been established supporting a presumption that atrazine is a genotoxic agent capable of initiating neoplasia or inducing transmissable mutation in mammalian germ cells."

However, Dearfield (1988) evaluated Brusick's report for the Agency and indicated the following:

"It appears from a review of the many atrazine studies available to OPP from submissions and through the published literature that atrazine does not induce genotoxic activity in in vitro studies with or without mammalian activation systems. However, there does appear to be genotoxic potential by atrazine as revealed in in vivo studies (aberrations in mouse bone marrow and a dominant lethal assay). These results suggest a mutagenicity concern for atrazine as well as for possible heritable effects. The regulatory requirements for atrazine have not been fulfilled by registrant submissions and the categories not fulfilled include: (1) structural chromosome aberrations and (2) other genotoxic effects. Since the publisned literature provides suggestions of positive in vivo effects, it is suggested that atrazine be at least tested adequately in an in vivo system for aberrations and for dominant letnal effects.

The conclusion Brusick presents in his document does not totally agree with the regulatory position outlined above. The weight-of-evidence scheme he uses to a assess atrazine genotoxicity is based on examining all test results, providing each result with various weighting factors (e.g., dose, magnitude of response, phylogenetic level of test organism, etc.) and then reducing all results to a final agent score. The consensus score for atrazine was in the 16 to 20 range which suggested to Brusick a non-mutagenic status. It should be emphasized that this score is the result of combining all test results into a consensus trend towards negative or positive activity. It is agreed that the bulk of atrazine data is negative and that this score would tend towards a negative trend. However, the positive in vivo studies should not be overlooked and on a scientific basis, these findings have not been diminished by other atrazine studies. Other concerns involving the scheme Brusick used are a lack of calibration of agent test scores to an external standard and the use of data evaluated by the Agency as being unacceptable to help generate the final atrazine score.

A final major consideration is the role that plant metabolism plays in the genotoxicity of atrazine. It is established that atrazine is a plant

activated promutagen. This may be a concern to individuals who consume atrazine treated products. There is limited evidence to suggest that metabolites generated by plant metabolism produce effects in mammalian cells. The further characterization of the role of plant metabolism towards possible mammalian genotoxic hazard needs to be examined."

In the guidance for registration of atrazine products (U.S. EPA, 1989), the agency suggests carrying out additional studies including a dominant letnal study and a study seeking evidence for or against direct DNA damage, especially in view of the high potential for human exposure to atrazine.

E. CARCINOGENICITY

Innes et al. (1969) investigated the potential of atrazine for tumorigenicity in mice ranging in age from 7 to 28 days. Two F_1 hybrid stocks (C57BL/6 x C3H/AnF) and (C57BL/6 x AKR) were used. A dose of 21.5 mg/kg of atrazine (the maximum tolerated dose) was administered in 0.5% gelatin by stomach tube to 18 mice of each sex from each strain (72 mice in total). The dose was not readjusted to account for weight gain. After weaning at 4 weeks, this same dose level (21.5 mg/kg/day) was maintained by feeding 82 ppm atrazine ad libitum in the diet for 18 months. At necropsy, thoracic and abdominal cavities were examined and histologic studies performed on all major organs and grossly visible lesions. Blood smears were examined if the mice showed signs of splenomegaly or lymphadenopathy. The incidence of hepatomas, pulmonary tumors, lymphomas, and total tumors in atrazine-treated mice was not significantly different from the negative controls.

In a carcinogenicity study conducted by Industrial Bio-Test Laboratories (IBT, 1981), Swiss white mice were given atrazine in their feed at doses of 0, 10, 300, or 1,000 ppm (0, 1.5, 45, or 150 mg/kg/day, respectively). Each group consisted of 60 male and 60 female mice. Males were treated for 21 months and females for 22 months. The highest dose of atrazine (1,000 ppm) resulted in

decreased body weights in both males and females and decreased survival in females. No gross pathology was found in any of the groups, and there was no histopathologic indication of any inflammatory, degenerative, proliferative, or neoplastic lesions associated with atrazine treatment.

The data submitted by IBT (1981) have been evaluated by EPA, and a number of deficiencies have been found. There were no diet preparation records to verify that the animals received the test material in the diet during the first 6 months of the study, and analysis of dietary concentrations and stability of atrazine in the diet indicated that for the first year of the study the animals probably received lower dose levels than those required by the protocol. In addition, clinical observations and mortalities recorded were limited mainly to collective group notations for the first 16 months of the study. Therefore, the results of the study cannot be considered definitive, but must be considered as only supplementary to other chronic toxicity and oncogenicity studies.

In oncogenicity studies carried out by Hazleton Laboratories, Inc. (1961), atrazine was fed to male and female rats for 2 years. The rats were divided into four groups that received 0, 1, 10, or 100 ppm (0, 0.05, 0.50, or 5.0 mg/kg/day, respectively) atrazine in their food. Each group contained 30 male and 30 female rats. After 65 weeks, the 1.0-ppm atrazine dose was increased to 1,000 ppm (50 mg/kg/day) for the remainder of the study. Five males and five females from each group were randomly chosen and sacrificed after 26 and 52 weeks. At necropsy, the following organs were collected and preserved: brain, pituitary, thyroid, heart, lung, liver, kidney, adrenal, spleen, stomach, pancreas, small and large intestine, bladder, testes or ovary, bone marrow, skeletal muscle, and peripheral nerve. Blood hematocrits and leukocyte counts were determined, and urinalyses for sugar, protein, bile pigments, and pH were

performed. Atrazine had no effects on the general appearance or behavior of the rats. A transient roughness of the coat and piloerection in some animals were observed after 20 weeks of treatment at the 10- and -ppm doses, but not at 52 weeks. Body weight gains, food consumption, and survival were similar in all groups for the first 18 months; from 18 to 24 months there was high mortality in all groups. There were no differences among the groups in hematology, patnology, or urinalyses. Microscopic examination of both males and females revealed no differences in tumor development between treated and control animals for animals sacrificed at 52 or 104 weeks, for animals dying, or for the total numbers of all tumors.

This study cannot be considered adequate to delineate the oncogenic potential of atrazine. Very few animals of either sex remained alive at 104 weeks, probably due to the intercurrent infection noted by the laboratory. The paucity of animals examined, the poor viability due to the infection race of those on test, and the failure to analyze feed for the active ingredient limit the applicability of this study.

The 91-week oral feeding/oncogenicity study (experimental details are described in Section V.B) in mice performed by Ciba-Geigy (1987c) has been evaluated by the Agency. In this study, atrazine (97% a.i.) was fed to 5-week-old CD-1 male and female mice weighing 26.8 and 21.0 g, respectively. The mice were randomly assigned to five experimental groups of approximately 60 animals/sex/group. The dosages tested were 0, 10, 300, 1,500, and 3,000 ppm; these dosages correspond to an actual mean daily atrazine intake of 1.4, 38.4, 194.0, and 385.7 mg/kg/day for males, and 1.6, 47.9, 246.9, and 482.7 mg/kg/day for females. Atrazine was not oncogenic in this strain of mice. No dose-related increases in the incidence of neoplasms were noted in this study.

Palpable masses in three female mice (one mouse in the control group and two mice fed chow containing 3,000 ppm atrazine) were mammary adenocarcinomas. One female in the 1[illegible]-ppm exposure group developed a fibroma, and one female in the 300-ppm group developed malignant lymphoma. Two male mice fed 10 ppm atrazine developed fibrosarcomas. One male mouse in the 1,500-ppm exposure group developed a hemangiosarcoma (a malignancy formed by the proliferation of endothelial and fibroblastic tissue). These neoplasms were found after histological examination of palpable masses in mice. In male mice fed 10 ppm atrazine, a statistically significant increase in the incidence of hepatocelllular adenomas was observed, yet no statistically significant increase in incidence of this type of tumor was observed in groups of mice fed higher levels of atrazine (i.e., 300 ppm, 1,500 ppm, or 3,000 ppm). The effect was not dose-related. No statistically significant increases in incidence were found for the following types of neoplasms: mammary adenocarcinomas, adrenal adenomas, pulmonary adenomas, and malignant lymphomas.

A two-year feeding/oncogenicity study in rats by Ciba-Geigy (1986) has been evaluated recently by the Agency. Atrazine (98.9% a.i.) was fed to 37- to 38-day-old Sprague-Dawley rats. The dosage levels used were 0, 10, 70, 500 or 1,000 ppm, equivalent to 0, 0.5, 3.5, 25 or 50 mg/kg/day (using Lehman's conversion factor, 1959). The total number of animals/sex in the control and HDT groups was 90; and 70 animal/sex/group for the 10, 70 and 500 ppm groups. Histopathology was performed on all animals. In females, atrazine was associated with a statistically significant increase in mammary gland fibroadenomas at 1,000 ppm, in mammary gland adenocarcinomas (including two carcinosarcomas at the HDT) at 70, 500 and 1,000 ppm, and in total mammary gland tumor bearing animals at 1,000 ppm. Each of these increases was associated with a statistically significant dose-related trend and was outside of the high end of the historical

control range. In addition, analysis of data of the one year interim report on this study (Ciba-Geigy, 1985) indicated that there was evidence for decreased latency for mammary gland adenocarcinomas. This study was also reported as positive in a briefing paper by Ciba-Geigy (1987d). Table V-9 reflects the increased incidence of the mammary tumors in females in this study. However, this Table was recently updated (U.S. EPA, 1988) due to minor error in the number of animals examined; the tumors were further analyzed using the Peto Prevalence method since survival differences were observed in the female rats, see Table V-10 for the updated incidence of these tumors.

Administration of atrazine to the female rats was associated with a statistically significant ($p < 0.05$) increase in mammary gland fibroadenomas at 1,000 ppm, in mammary gland adenocarcinomas (including two carcinosarcomas at the highest doses tested) at 70, 500 and 1,000 ppm, and in total mammary gland tumor-bearing animals at 1,000 ppm. Each of these increases was associated with a statistically significant dose-related trend and was outside the high end of the historical control range. In addition, there was evidence for decreased latency for mammary gland adenocarcinomas at the 12-month interim sacrifice. A statistically significant increase in testicular interstitial cell tumors was seen in male Sprague-Dawley rats at 1,000 ppm; however, this increase was within the historical control range. In both males and females, the highest dose tested exceeded the MTD based upon body weight gain decrement in males and increased mortality, liver necrosis, and bone marrow myeloid hyperplasia in the females. The MTD was reached in males and females at 500 ppm (25 mg/kg/day).

Table V-9. Mammary Tumors in Female Rats Fed Atrazine for 2 Years

	Dose level (ppm)				
	0	10	70	500	1000
12-month sacrifice/deaths and moribund sacrifices at 0 to 13 months					
No. tissues examined	12	5	1	5	15
Adenocarcinoma	0	1	1	0	3
Fibroadenoma	0	0	1	1	1
13-month sacrifice					
No. tissues examined	10	--	--	--	10
Adenocarcinoma	0	--	--	--	5
Fibroadenoma	0	--	--	--	2
Terminal sacrifice/deaths and moribund sacrifices at 13 to 24 months					
No. tissues examined	66	64	68	65	65
No. rats - adenocarcinoma and carcinosarcoma	15	15	26	27	37
No. of adenocarcinomas	17	22	42	48	64
No. rats - fibroadenoma	29	29	35	38	42
No. of fibroadenomas	37	46	48	81	69
Mammary tumor-bearing rats	35	39	47	47	56
All animals on study					
No. of tissues	88	69	69	70	89
Carcinomas	15	16	27	27	45
Adenomas and fibroadenomas	29	29	36	39	46
All tumors	35	40	48	48	65
p values[a]					
Carcinomas:					
Cox-Tarone			0.0454	0.0071	<0.00005
Genan Breslow			0.0290	0.0016	<0.00005
Adenomas and fibroadenomas:					
Cox-Tarone				0.0685	0.0004
All tumors:					
Cox-Tarone				0.0071	<0.00005
Genan-Breslow				0.0050	<0.00005

[a]Life-table analysis, pairwise comparison.

SOURCE: Adapted from Ciba-Geigy (1986).

Table V-10. Female Rat Mammary Tumor Rates* and Peto's Prevalence Test Results

DOSE		0.	10.	70.	500.	1,000.
BENIGN		20/88	25/65	21/69	21/68[a]	20/89[b]
	(%)	(23)	(37)	(30)	(31)	(22)
	(p)	0.446	0.110	0.373	0.373	0.468
MALIGNANT		15/88	16/67[c]	27/69	27/68	45/89[d]
	(%)	(17)	(24)	(39)	(40)	(51)
	(p)	0.000##	0.390	0.024#	0.019#	0.000##
BENIGN AND MALIGNANT COMBINED		35/88	40/67	48/69	48/68	65/89
	(%)	(40)	(60)	(70)	(71)	(73)
	(p)	0.000##	0.111	0.017#	0.015#	0.000##

* Number of tumor bearing animals/Number of animals at risk. (Excluding animals that died before the observation of the first tumor or animals not examined).

() Percent

a First adenoma occurred at 81 weeks in dose 500 ppm.
b First fibroadenoma occurred at 45 weeks in dose 1,000 ppm.
c First adenocarcinoma occurred at 34 weeks in dose 10 ppm.
d First carcinosarcoma occurred at 69 weeks in dose 1,000 ppm.

NOTE: Significane of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. # denotes - <0.05; and ## denotes p <0.01.

F. SUMMARY

Acute oral LD_{50} values for atrazine in hamsters, rats, and mice range from 672 to 3,000 mg/kg. Toxic signs reported to accompany acute exposure include ataxia, diarrhea, oral discharge, and chromorhinorrhea, with histological changes in the lungs, heart, liver, spleen, kidneys, and brain. In one study, atrazine was far less acutely toxic to weanling than to adult rats. Atrazine produces moderate to slight eye and skin irritation but not dermal sensitization.

In short-term studies, no effect was observed in mice fed doses of atrazine up to 150 mg/kg/day for 28 days. Doses of 450 mg/kg/day resulted in 2/10 deaths but no evidence of gross pathology, and doses of 1,500 or 4,500 mg/kg caused weight loss, muscle weakness, tremors, and increased mortality. Doses of 100 mg/kg were reported to cause hypotension in cats and antidiuresis in dogs.

In one study in sheep, doses of 5 mg/kg/day for 10 days produced ataxia, anorexia, and histopathologic signs in the kidneys, liver, and lungs. In another study in sheep, doses up to 25 mg/kg/day for 5 weeks produced no visible effects; however, doses of 50 mg/kg/day caused weight loss, and doses of 100 to 400 mg/kg/day caused lethality. Cattle and sheep fed hay from a field sprayed with atrazine (average daily atrazine intake of about 20 to 40 mg/kg/day) showed no significant change in weight gain, clinical chemistry, or histologic appearance of tissues.

In studies on functional changes induced by short-term feeding of atrazine, the feeding of 100 to 600 mg/kg/day to rats for 14 days affected kidney function, leading to increased elimination of electrolytes and decreased creatinine clearance. No behavioral changes were noted in rats fed 37.5 or 75 mg/kg/day 6 weeks.

In longer term studies, mice fed 38.4 mg atrazine/kg/day for 91 weeks showed no signs or symptoms of toxicity. At doses of 194 and 384 mg/kg/day, however, both male and female mice exhibited decreases in mean body weight gain, erythrocyte count, hematocrit, and hemoglobin, and females had an increased incidence of cardiac thrombi. Rats fed 5 mg/kg/day for 183 days showed no significant effects except for a small decrease in weight gain among female rats after 182 days. At higher levels of atrazine, reports of toxicity in rats are equivocal: one study described only decreased weight gain after feeding for 6 months at 25 mg/kg/day, a second study indicated marked lethality and severe morphological changes in rats given 20 mg/kg/day for the same time period, and a third study showed reduced weight gain, hypercholesterolemia, and hematologic changes in rats fed 140 or 280 mg/kg/day chronically (time not indicated).

In a chronic toxicity/oncogenicity study, male and female rats fed 10, 70, 500, and 1,000 ppm atrazine in the diet for 2 years exhibited significant differences in clinical hematological and tissue parameters from control animals only at the two highest doses, which were above the maximum tolerated dose. This study demonstrated a LOAEL of 500 ppm (25 mg/kg/day) and a NOAEL of 70 ppm (3.5 mg/kg/day), based on decreased body weight gain. However, oncogenic activities were noted at 70 ppm and above as reflected in the increased incidence of mammary gland tumors in females, but no remarkable oncogenic activities were noted at the lowest dose tested 10 ppm (0.5 mg/kg/day).

Dogs fed 0.35 mg atrazine/kg/day for 105 weeks showed no adverse effects; in the same study, dogs fed 3.5 mg/kg/day had decreased food intake, and dogs fed 35 mg/kg/day showed decreased food intake, weight loss, increased adrenal weight, decreased hematocrit, and occasional tremors or stiffness in hind limbs. In another study, dogs fed atrazine in the diet at 150 ppm (approximated

to 5 mg/kg/day) for 52 weeks produced significantly decreased P-II waves in females at day 175 of the study and cardiac toxicity in two male dogs; at 1,000 ppm (approximated to 34 mg/kg/day), significant EKG alterations and moderate to severe cardiac lesions were observed (NOAEL, 0.5 mg/kg/day; LOAEL, 5 mg/kg/day). A further detailed analysis of the individual animal data revealed that the effects observed at 5 mg/kg/day were not likely to be atrazine-related. Therefore, the NOAEL and the LOAEL from this tudy are 5 mg/kg/day and 34 mg/kg/day, respectively (Copley, 1988).

Several adequate studies on reproduction and developmental toxicity have been conducted. Doses of 2.5 or 5 mg/kg/day had no measurable effect on reproduction in a three-generation feeding study in rats. However, in a more recent two-generation rat study, maternal toxicity and reduced pup weight in F_2 generation were noted at 2.5 (maternal toxicity NOAEL) and 25 mg/kg/day (maternal toxicity LOAEL); no adverse effect on reproduction was noted at 0.5 mg/kg/day (reproductive NOAEL). The reproductive LOAEL was 2.5 mg/kg/day based on reduced pup weight. Doses of 10 mg/kg/day had no measurable fetotoxicity when given orally to pregnant rats on days 6 to 15 of gestation; doses of 70 or 700 mg/kg/day caused fetal or maternal toxicity and lethality. Rats fed doses up to 40 mg/kg/day throughout gestation showed no effects on litter size or weight. Subcutaneous injection of 46.4 mg/kg/day of atrazine in pregnant mice on days 6 to 15 of pregnancy did not produce a significant increase in fetal anomalies. Subcutaneous injections of doses up to 200 mg/kg/day in pregnant rats on gestational days 3, 6, and 9 had no effect on litter size; however, doses of 800 or 2,000 mg/kg/day were embryotoxic. Rabbits receiving 1, 5, or 75 mg/kg atrazine by gavage on days 7 through 19 of gestation showed maternal

toxicity at the two higher doses, but developmental toxicity occurred only at 75 mg/kg. The data indicate that atrazine is not embryotoxic except when administered at relatively high levels, at which substantial maternal toxicity occurs.

Atrazine does not induce genotoxicity in *in vitro* studies with or without mammalian activation systems but can be converted by plant microsomes to a form that is mutagenic in prokaryotes and eukaryotes. *In vivo* somatic and germinal cell cytogenetic assays are equivocal, and no acceptable assays evaluating other mutagenic mechanisms were found. Brusick (1987), using the ICPEMC weight-of-evidence scheme for assessing multitest mutagenicity studies (Brusick et al., 1986; Brusick et al., 1987), concluded that atrazine, with a consensus score of about 16 to 20, should be given a "nonmutagenic status." However, Dearfield (1988) challenged the use of the scheme on the basis that the data were not calibrated against an external standard, the scheme is developmental and presumably will require further refinements as the data base grows, and the data have not been correlated to existing bioassay systems. Dearfield also questioned the final atrazine score, he acknowledged that the bulk of the atrazine data was negative and a negative trend would be expected; however, the use of some of the flawed negative studies in this scheme casts doubts on the validity of the atrazine assessment using the weight of evidence approach at the present time.

Brusick's reviews tend to agree with Dearfield's statement that evidence from the positive *in vivo* studies that suggests that atrazine may represent a potential health hazard should not be ignored and has not been disproven by other atrazine studies. However, until atrazine is adequately tested in *in vivo* cytogenetic assays and in studies that examine other mutagenic mechanisms,

a consensus conclusion on the genotoxicity of atrazine is not possible. The agency indicates that additional mutagenicity studies including a dominant lethal study and a study seeking evidence for or against DNA damage be carried out in view of the high potential for human exposure to atrazine.

Studies on the oncogenicity of atrazine are equivocal. No evidence of increased tumor frequency was observed in mice fed 21.5 mg/kg/day of atrazine for 18 months or in mice fed up to 150 mg/kg/day for 21 to 22 months, although the latter study is of questionable validity. On the other hand, in a recent study with Sprague-Dawley rats fed 10 to 1,000 ppm atrazine (0.5 to 50 mg/kg/day) in the diet for 2 years, female rats had statistically significant increases in mammary carcinomas over control rats at atrazine levels of 70 ppm (3.5 mg/kg/day) and above. Moreover, an increased incidence of mammary tumors was apparent by 13 months. Male rats showed an increase in testicular interstitial cell tumors at the 1,000-ppm dose level; however, this increase was within the historical control range. Based on this positive response in the Sprague-Dawley rats and considering that closely related analogs of atrazine (propazine, simazine and terbutryn) caused tumors in the same target organ (mammary gland) in the same strain of rats, atrazine may be classified in Group C: possible human carcinogen according the EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a).

VI. HEALTH EFFECTS IN HUMANS

A. CLINICAL CASE STUDIES

Very few studies were found in the available literature that describe the effects of atrazine in humans. Schlicher and Beat (1972) reported a case of severe contact dermatitis in a 40-year-old farm worker who developed a painful erythematous eruption with blistering of both hands and forearms after cleaning the nozzles of a spray rig with his bare hands during the use of atrazine.

B. EPIDEMIOLOGICAL STUDIES

Lony et al. (1969) published a preliminary report of a cohort study to ascertain the effects of pesticides in humans. The study was limited to 33 farmers (15 with high usage and 18 with low usage of pesticides) divided into two groups. A wide range of pesticides had been used, including 9 animal insecticides, 8 crop insecticides, and 12 herbicides. Atrazine was the third most widely used herbicide. Significant correlations ($p < 0.01$) were obtained when the amount of atrazine employed by the high-use group was compared with the 1- and 30-minute bilirubin values. The number of subjects was small, however, and confounding factors were present, raising questions about the significance of the results.

Yoder et al. (1973) examined chromosomes in lymphocyte cultures taken from 26 agricultural workers exposed to herbicides. Atrazine was third among the 14 herbicides most commonly used. Sixteen unexposed individuals served as controls. More chromosome aberrations were found in the workers during midseason exposure to herbicides than during the off-season for spraying. This was manifested by a 4-fold increase in chromatid gaps and a 25-fold increase in chromatid breaks (Table VI-1). During the off-season, the mean number of gaps

Table VI-1. Seasonal Variation in the Occurrence of Chromatid Lesions in Human Lymphocytes

Group	Number	Chromatid gaps[a]		Chromatid breaks[a]	
		Off-season	Midseason	Off-season	Midseason
Control	16	0.63±0.22[b] (0–3)[c]	0.69±0.24 (0–3)	0.31±0.12 (0–1)	0.44±0.22 (0–3)
Herbicide-exposed	26	0.38±0.10[b] (0–1)[c]	1.38±0.22 (0–5)	0.07±0.05 (0–1)	1.81±0.35 (0–6)

[a]Per person per 25 cells scored.
[b]Mean ± SE.
[c]Range.

SOURCE: Adapted from Yoder et al. (1973).

and breaks was lower in the herbicide-exposed group than in the controls, who were in occupations unlikely to involve herbicide exposure. The authors suggested that chromosomal repair is enhanced during periods without exposure, resulting in compensatory protection. Since the data are confounded by the large number of herbicides used, the contribution of atrazine to increased development of chromatid breaks and gaps cannot be determined.

C. HIGH-RISK GROUPS

No information was found in the available literature concerning groups at high risk.

D. SUMMARY

Little information is available on the health effects of atrazine in humans. One case report indicated that a farmer with a past history of reactions to propachlor suffered from contact dermatitis after exposure to atrazine. One epidemiological study with a small number of Iowa farmers reported some correlation between atrazine useage and increased 1- and 30-minute bilirubin values. In another study, increased chromosomal aberrations were reported in agricultural workers who used atrazine and other pesticides. The available data did not identify any subpopulation more sensitive to atrazine than the general population.

VII. MECHANISMS OF TOXICITY

Although there have been a number of studies on the mechanism of action of triazine herbicides in plants, there are very few studies to determine the mechanism of atrazine toxicity on mammalian cells and organisms. In one study, Walker et al. (1979) evaluated the effects of atrazine in Ehrlich ascites tumor cells *in vivo* and *in vitro*. Daily intraperitoneal (ip) injection of atrazine dissolved in dimethylsulfoxide (DMSO) for 6 to 8 days, at levels of 120 to 140 mg/kg/day, produced 30 to 40% inhibition of tumor development in BALB/c mice. At the molecular level, atrazine had an effect on *de novo* purine synthesis *in vivo*, inhibiting the incorporation of formate-^{14}C into ascites tumor cell purines when administered at dose levels of 100 to 200 mg/kg. The inhibitory effect was most prominent 2 to 12 hours after injection, was clearly visible after 24 hours, and was still detectable after a 36-hour interval of exposure. Incubation of ascites tumor cells with atrazine *in vitro* led to inhibition of incorporation of radiolabeled precursors of DNA, RNA, and protein into the cells. The degree of inhibition ranged from 4 to 13% at an atrazine concentration of 10^{-5} M, from 29 to 50% at 10^{-4} M, and rose to 94 to 99% inhibition at an atrazine concentration of 10^{-3} M. One possible mechanism of action of atrazine in mammalian cells may therefore be interference with nucleic acid metabolism.

Messner et al. (1979) determined the effect of atrazine on rat liver cyclic adenosine monophosphate (AMP) and glycogen phosphorylase activity. Atrazine, suspended in corn oil, was administered ip to adult female Sprague-Dawley rats at a dose level of 250 mg/kg. There was a threefold increase in the liver cyclic AMP level that reached a peak 4 hours after injection and then declined. The increase in cyclic AMP level was followed after a lag period of about 1 hour by a threefold increase in the activity of glycogen phosphorylase.

Concomitantly, the liver glycogen level decreased and the blood glucose level rose. There were, however, no substantial changes in the activities of adenylate cyclase or of phosphodiesterase in the liver 4 hours following atrazine administration. *In vitro*, utilizing isolated hepatocytes, atrazine alone had only a small effect on basal cyclic AMP level; however, the herbicide caused a significant increase in the glucagon-stimulated cyclic AMP level, producing at least three times the response to the hormone. These studies indicate that atrazine may exert an effect on glycogen metabolism in the mammalian organism.

B. SUMMARY

There is some evidence to indicate that atrazine may interfere with nucleic acid metabolism. This is based on the observed *in vivo* inhibition of incorporation of labeled formate into purines of Ehrlich ascites tumor cells in BALB/c mice injected intraperitoneally with atrazine. Atrazine also inhibited *in vitro* incorporation of radiolabeled precursors of DNA, RNA, and protein into ascites tumor cells. Based on *in vivo* studies in rats on the effect of atrazine on rat liver cyclic adenosine monophosphate (AMP) and glycogen phosphorylase activity, atrazine may also exert an effect on glycogen metabolism in mammalian organisms. Atrazine produced a significant increase in the glucogen-stimulated cyclic AMP level *in vitro* in isolated hepatocytes.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of separate assessments of noncarcinogenic and carcinogenic effects. Chemicals that do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic health effects occur, while carcinogens are assumed to act without a threshold.

A. PROCEDURES FOR QUANTIFICATION OF TOXICOLOGICAL EFFECTS

1. Noncarcinogenic Effects

In the quantification of noncarcinogenic effects, a Reference Dose (RfD, formerly called the Acceptable Daily Intake (ADI)) is calculated. The RfD is an estimate (with an uncertainty spanning perhaps an order of magnitude) of a daily exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious health effects during a lifetime. The RfD is derived from a No-Observed-Adverse-Effect Level (NOAEL), or Lowest-Observed-Adverse-Effect Level (LOAEL), identified from a subchronic or chronic study, and divided by an uncertainty factor(s). The RfD is calculated as follows:

$$RfD = \frac{(NOAEL \text{ or } LOAEL)}{\text{Uncertainty factor(s)}} = ___ \text{ mg/kg bw/day}$$

Selection of the uncertainty factor to be employed in the calculation of the RfD is based on professional judgment while considering the entire data base of toxicological effects for the chemical. To ensure that uncertainty factors are selected and applied in a consistent manner, the Office of Drinking Water (ODW) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980) as follows:

- An uncertainty factor of 10 is generally used when good chronic or subchronic human exposure data identifying a NOAEL are available and are supported by good chronic or subchronic toxicity data in other species.

- An uncertainty factor of 100 is generally used when good chronic toxicity data identifying a NOAEL are available for one or more animal species (and human data are not available), or when good chronic or subchronic toxicity data identifying a LOAEL in humans are available.

- An uncertainty factor of 1,000 is generally used when limited or incomplete chronic or subchronic toxicity data are available, or when good chronic or subchronic toxicity data identifying a LOAEL, but not a NOAEL, for one or more animal species are available.

The uncertainty factor used for a specific risk assessment is based principally on scientific judgment rather than scientific fact and accounts for possible intra- and interspecies differences. Additional considerations, which may necessitate the use of an additional uncertainty factor of 1 to 10, not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less-than-lifetime study for deriving an RfD, the significance of the adverse health effect, pharmacokinetic factors, and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL represents a medium-specific (i.e., drinking water) lifetime exposure, at which adverse, noncarcinogenic health effects are not anticipated to occur. The DWEL assumes 100% exposure from drinking water. The DWEL provides the noncarcinogenic health effects basis for establishing a drinking water standard.

For ingestion data, the DWEL is derived as follows:

$$DWEL = \frac{RfD \times (\text{body weight in kg})}{\text{Drinking water volume in L/day}} = ____ \text{ mg/L } (____ \text{ ug/L})$$

where:

Body weight = assumed to be 70 kg for an adult.

Drinking water volume = assumed to be 2 L per day for an adult.

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (One-day, Ten-day, and Longer-term) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using an equation similar to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (bw)}{(UF) \times (___ \text{ L/day})} = ____ \text{ mg/L } (____ \text{ ug/L})$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. One-day HA for a 10-kg child ingesting 1 L water per day.
2. Ten-day HA for a 10-kg child ingesting 1 L water per day.
3. Longer-term HA for a 10-kg child ingesting 1 L water per day.
4. Longer-term HA for a 70-kg adult ingesting 2 L water per day.

The One-day HA calculated for a 10-kg child assumes a single acute exposure to the chemical and is generally derived from a study of less than 7 days duration. The Ten-day HA assumes a limited exposure period of 1 to 2 weeks and

is generally derived from a study of less than 30 days duration. The Longer-term HA is derived for both a 10-kg child and a 70-kg adult and assumes an exposure period of approximately 7 years (or 10% of an individual's lifetime). The Longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of an animal's lifetime).

2. Carcinogenic Effects

The EPA categorizes the carcinogenic potential of a chemical, based on the overall weight of evidence, according to the following scheme:

- Group A: Human Carcinogen. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.

- Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.

- Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.

- Group D: Not Classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.

- Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

If toxicological evidence leads to the classification of the contaminant as a known, probable, or possible human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these estimates usually come from lifetime exposure studies in animals. To predict the risk for humans from animal data, animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous exposure, less-than-lifetime studies, and for differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg, and that the average water consumption of an adult human is 2 liters of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure via ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with a 95% upper confidence limit providing a low dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit, and probit. There is little basis in the current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than any others. Because each model is based on differing assumptions, the estimates that are derived for each model can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty due to the systematic and

random errors in scientific measurement. In most cases, only studies using experimental animals have been performed. Thus, there is uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist, such as the incomplete knowledge concerning the health effects of contaminants in drinking water; the impact of the experimental animal's age, sex, and species; the nature of the target organ system(s) examined; and the actual rate of exposure of the internal targets in experimental animals or humans. Dose-response data usually are available only for high levels of exposure, not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

B. QUANTIFICATION OF NONCARCINOGENIC EFFECTS FOR ATRAZINE

1. One-day Health Advisory

It is concluded that although there are numerous acute toxicity studies which determined lethality (e.g., LD_{50}), there is only one article (Russian) indicating that a single dose of 100 mg/kg results in hypotension. No suitable information was found in the available literature for the determination of the One-day HA value for atrazine. In the absence of suitable acute toxicity data, it is recommended that the Ten-day HA value determined from the developmental toxicity study in rabbits (Ciba Geigy, 1984b) be used to develop a conservative estimate of the One-day HA value for atrazine. The One-day HA value for a 10-kg child is 0.1 mg/L (100 ug/L).

2. Ten-day Health Advisory

In the absence of other suitable short-term toxicity studies, the effects of atrazine on gestating females, in assessment of developmental toxicity, are

suitable for estimation of the Ten-day HA for atrazine. Of the studies on reproductive and teratogenic effects described in Section V.C, Reproductive/Teratogenic Effects, and included in Table V-6, those by Ciba-Geigy (1984a), with rats and rabbits, most carefully determined the effects on gestating females. In these studies, atrazine was administered by gavage to female rats during gestation days 6 to 15 (10 days) and to rabbits during gestation days 7 to 19 (13 days). A NOAEL of 10 mg/kg for maternal toxicity was established for the rat, and a NOAEL of 1 mg/kg for maternal toxicity was established for the rabbit in these studies, both based on reduced body weight gains. Thus, the rabbit appears to be a more sensitive species than the rat for maternal toxicity. The NOAEL of 1 mg/kg in the rabbit, as the more conservative value, is selected for use as the basis for calculation of the Ten-day HA.

The Ten-day HA for a 10-kg child is calculated as follows:

$$\frac{(1.0 \text{ mg/kg/day})(10 \text{ kg})}{(1 \text{ L/day})(100)} = 0.1 \text{ mg/L } (100 \text{ ug/L})$$

where:

1.0 mg/kg/day = NOAEL, based on absence of adverse effects in female rabbits given atrazine by gavage during days 7 to 19 of gestation.

100 = uncertainty factor, chosen in accordance with EPA and NAS guidelines for use with a NOAEL from an animal study.

10 kg = assumed weight of child.

1 L/day = assumed water consumption of a 10-kg child.

3. Longer-term Health Advisory

No suitable information was found in the available literature for the determination of the Longer-term HA values for atrazine. It is therefore recommended that the adjusted DWEL for a 10-kg child of 50 ug/L and the

DWEL for a 70-kg adult of 200 ug/L be used at this time as conservative estimates of the longer-term HA.

4. Reference Dose and Drinking Water Equivalent Level

Table VIII-1 summarizes the studies considered for derivation of the RfD and DWEL for atrazine. In a 6-month feeding study in rats, conducted by Suschetet et al. (1974), a NOAEL of 5 mg/kg/day and a LOAEL of 25 mg/kg/day can be identified, based on reduced food intake and growth retardation. It cannot be established, however, whether the reduced food intake was due to atrazine toxicity or taste aversion. In the 91-week feeding study in mice, a NOAEL of 38.4 mg/kg/day was identified; the study also identified a LOAEL of 194 mg/kg/day based on decreases in mean body weight gain, erythrocyte count, hematocrit, and hemoglobin in males and females, and an increased incidence of cardiac thrombi in females (Ciba-Geigy, 1987c). In reviewing these data, mice appear to be less sensitive to atrazine than other animals.

The 2-year Woodard Research Corporation (1964) study in dogs reflected a NOAEL of 0.35 mg/kg/day and a LOAEL of 3.5 mg/kg/day for chronic atrazine toxicity, based on increased heart and liver weights in females. Only four dogs/sex/dose were used, information on the purity of atrazine used was absent, and hematological data were inadequately documented. EPA considers this study to be partially flawed. A 52-week oral study in beagle dogs (Ciba-Geigy, 1987b) used technical-grade atrazine (97% pure). This study was considered to reflect a NOAEL of 0.5 mg/kg/day and a LOAEL of 5 mg/kg/day based on mild cardiac pathology intensified at the higher dose tested, 34 mg/kg/day for males and females. However, based on the additional information supplied by Ciba-Geigy (discussed in Section V.B) clarifying the relationship between severe

Table VIII-1. Summary of Candidate Studies for Derivation of the Reference Dose and Drinking Water Equivalent Level for Atrazine

Reference	Species	Route	Exposure duration	Endpoints	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
Suschetet et al. (1974)	Rat	Oral (feed)	183 days	Food intake; body weight; histology	5	25
Ciba-Geigy (1987c)	Mouse	Oral (feed)	91	Weight gain; hematology; cardiac pathology	38.4	194
Woodard Research Corporation (1964)	Dog	Oral (feed)	105 weeks	Food intake; weight gain; organ weights; histology	0.35	3.5
Ciba-Geigy/ Copley (1987b,1989)	Dog	Oral (food)	52 weeks	EKG; cardiac pathology; histology	5.0	34
Ciba-Geigy (1986)	Rat	Oral (food)	2 years	Body weight; hematology histology; clinical chemistry; organ weights	3.5*	25
Ciba-Geigy (1987a)	Rat	Oral (food)	2-Gen.	Maternal toxicity; reduced pups' weight in F_2 generation	0.5	2.5

* Note that oncogenic activities were significant at this level; however, no remarkable increases in tumor incidence were noted at the lowest dose tested, 0.5 mg/kg/day.

potentially life-threatening lesions occurring at the high dose and the normal background variation unrelated to atrazine-treatment that occurred at the mid-dose, the NOAEL and the LOAEL were changed to 5 mg/kg/day and 34 mg/kg/day, respectively. The LOAEL was based on death, cachexia, ascites, decreased body weight and body weight gain, decreased food consumption, EKG changes, and cardiac lesions.

The well-executed 2-year chronic toxicity/oncogenicity study in rats (Ciba-Geigy, 1986) indicates a NOAEL of 3.5 mg/kg/day for non-oncogenic chronic toxicity and a LOAEL of 25 mg/kg/day, based on decreased body weight gain in both male and female rats. However, a significant increase in the incidence of mammary carcinomas was observed at these and higher doses when compared to controls. At the lowest dose of 0.5 mg/kg/day tested, there were no remarkable increases in tumor incidence or systemic effects.

The 2-generation rat reproduction study (Ciba-Geigy, 1987a) has been selected as the most appropriate study to derive Reference Dose (RfD) and Drinking Water Equivalent Level (DWEL). The parental systemic NOAEL in this study is 2.5 mg/kg/day, and the LOAEL is 25 mg/kg/day based on decreased body weight and body weight gain, and food consumption in both sexes throughout the study. The reproductive NOAEL and LOAEL are 0.5 mg/kg/day, and 2.5 mg/kg/day, respectively. The LOAEL is based on decreased body weight of pups in the second generation at the time of weaning (postnatal day 21). The latter values have been chosen as the basis for the determination of RfD and DWEL as they are the most conservative values. This is supported by the 2-year chronic feeding study in rats (Ciba-Geigy, 1986) in which neither systemic effects nor increased tumor incidences were observed at these dose levels. Additional support is evidenced from the 52-weeks old oral study with dogs (Copley, 1989)

in which the NOAEL and LOAEL values identified were 5 mg/kg/day and 34 mg/kg/day, respectively. These values are less protective than the above mentioned reproductive NOAEL and LOAEL of 0.5 mg/kg/day and 2.5 mg/kg/day, in rats (Ciba-Geigy, 1987a). Other studies (Woodard Research Corporation, 1966; Hazleton Laboratories, 1961; Ciba-Geiegy, 1987c) identified long-term NOAEL values of 5 to 50 mg/kg/day and were not considered to be as protective as the 2-generation rat study for use in calculating the HA values for atrazine.

Using the 2-generation study in rats (Ciba-Geigy, 1987a), the DWEL is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{0.5 \text{ mg/kg/day}}{100} = 0.005 \text{ mg/kg/day}$$

where:

0.5 mg/kg/day = NOAEL, based on the absence of decreased body weights of pups in the second generation at the time of weaning (postnatal day 21).

100 = uncertainty factor, chosen in accordance with EPA and NAS guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.005 \text{ mg/kg/day})(70 \text{ kg})}{2 \text{ L/day}} = 0.175 \text{ mg/L (rounded off to 200 ug/L)}$$

where:

0.005 = RfD

70 kg = assumed weight of an adult.

2 L/day = assumed water consumption of a 70-kg adult.

The proposed DWEL reflects the assumption that 100% exposure to atrazine is from drinking water. Since this chemical is used on food crops, the poten-

tial dietary exposure should be assessed. When the percentage contribution in the diet is determined, the DWEL should be adjusted to accommodate this factor in the determination of the MCLG. Also considering that atrazine is classified in Group C oncogen, an additional 10-fold uncertainty factor will be used in the calculation of the MCLG according to ODW policy to account for possible carcinogenicity.

C. QUANTIFICATION OF CARCINOGENIC EFFECTS FOR ATRAZINE

1. Categorization of Carcinogenic Potential

Data submitted by Ciba-Geigy (1986) on the chronic toxicity/oncogenicity study in rats indicate that atrazine induced an increased incidence of mammary carcinomas in female Sprague-Dawley rats. Male rats showed no increased incidence of any tumors. These findings have been further confirmed in a briefing by Ciba-Geigy (1987d) on this study. In this briefing, Ciba-Geigy also indicated that a study in Fisher 344 rats is currently under way. Atrazine was not oncogenic in mice (Ciba-Geigy, 1987c).

The International Agency for Research on Cancer has not yet evaluated the carcinogenic potential of atrazine (IARC, 1982); and no evidence is available regarding any carcinogenic potential of atrazine in humans.

Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), atrazine may be classified as Group C: Possible Human Carcinogen. This category is used for substances with limited evidence of carcinogenicity in animals in the absence of human data. Three closely related analogs, propazine, terbutryn, and simazine, are presently classified as Group C oncogens based on an increased incidence of tumors in the

same target tissue (mammary gland) and animal strain of rat (Sprague-Dawley) as was noted for atrazine.

2. Quantitative Carcinogenic Risk Estimates

No quantitative carcinogenic risk estimates of atrazine are presented in this document; however, the Office of Pesticide Programs is in the process of finalizing a quantitative risk assessment for atrazine. Since the chemical is classed as Group C oncogen, ODW policy uses an additional 10-fold uncertainty factor in the calculation of the MCLG to account for the possible carcinogenicity of atrazine.

D. EXISTING GUIDELINES AND STANDARDS

Toxicity data on atrazine were reviewed by NAS (1977), and the study by Innes et al. (1969) was used to identify a chronic NOAEL of 21.5 mg/kg/day. Although at that time it was concluded that atrazine has low chronic toxicity, an uncertainty factor of 2,000 was employed in calculation of the ADI from that study, since only limited data were available. The resulting value (0.021 mg/kg/day) corresponds to an ADI of 0.73 mg/L in a 70-kg adult consuming 2 liters of water per day.

Tolerances for atrazine alone and the combined residues of atrazine and its metabolites in or on various raw agricultural commodities have been established (U.S. EPA, 1986b). These tolerances range from 0.02 ppm (negligible) in animal products (meat and meat by-products) to 15 ppm in animal fodders (orchard grass and orchard grass hay).

E. SUMMARY

The recommended values for the One-day and Ten-day HAs are based on a NOAEL identified in a developmental toxicity study in rabbits. For a 10-kg child, the estimated value for these HAs is 100 ug/L. No suitable information was found upon which to base a Longer-term HA. Therefore, an adjusted DWEL was used to derive the Longer-term HA for a 10-kg child of 50 ug/L and for a 70-kg adult of 200 ug/L. The RfD and DWEL are based on a NOAEL identified in a 2-generation study with rats. The estimated values for the RfD is 0.005 mg/kg/day and for the DWEL is 200 ug/L. Since this chemical is used in food crops, the percentage contribution of atrazine in drinking water will be used to adjust the DWEL to accommodate this factor in the determination of the MCLG. In addition, considering that atrazine is classified as a Group C oncogen, an additional 10-fold uncertainty factor will be used in the calculation of the MCLG according to ODW policy to account for the possible carcinogenicity of this chemical.

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APPENDIX

Human Exposure

APPENDIX

Human Exposure

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A-2	Tolerances for Atrazine In and On Raw Agricultural Commodities	A-5

A variety of sources, including surface water, ground water, drinking water, food, ambient air, occupational settings, and consumer products, may expose humans to atrazine and other chemicals.

Atrazine has been found in 4,123 of 10,942 surface water samples analyzed and in 366 of 3,208 ground water samples (STORET, 1988). Samples were collected at 1,659 surface water locations and 3,208 ground water locations, and atrazine was found in surface water of 31 States and in ground water of 13 States. The 85th percentile of all non-zero samples was 2.3 ug/L in surface water and 1.9 ug/L in ground water sources. The maximum concentration was found to be 2,300 ug/L in surface water and 700 ug/L in ground water. Atrazine has also been found in ground water in Pennsylvania, Iowa, Nebraska, Wisconsin, and Maryland; typical positives were 0.3 to 3 ppb (Cohen et al., 1986). In a monitoring study of Mississippi River water, atrazine residues were found at a maximum level of 17 ppb; residues were detected throughout the year, with the highest concentrations found in June or July (Newby and Tweedy, 1976).

The following analysis of human exposure to atrazine is limited to drinking water, food, and ambient air because these media are considered to be sources common to all individuals. Even in limiting the analysis to these three sources, it must be recognized that individual exposure varies widely, based on personal choices and other factors over which little control exists Daily exposure and intake are profoundly affected by the geographic area in which a person lives, works, and travels; by an individual's diet; and by physiologic characteristics related to age, sex, and health status. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Detailed information concerning the occurrence of and exposure to atrazine in the environment was presented in an interim draft report by Johnston et al. (1984). The section that follows summarizes the pertinent information presented in that report for the purpose of assessing the relative source contribution of atrazine from drinking water, food, and air.

Available information on the range of human exposures to and intake of atrazine from drinking water, food, and ambient air for a 70-kg adult male is presented below. It would be difficult to estimate the number of individuals who experience specific combined exposures from these three sources.

A. EXPOSURE ESTIMATION

1. Drinking Water

Levels of atrazine in drinking water vary from one location to another. The highest concentration of atrazine monitored in the studies obtained was 15.9 ug/L in Ohio (Baker et al., 1981). The highest level of atrazine reported in national studies was 2.9 ug/L (Boland, 1981). Typical concentrations of atrazine in drinking water are lower. Analysis of the data in the National Screening Program for Organics in Drinking Water indicated that median levels of atrazine in drinking water systems are below 0.1 ug/L, since 86 of 116 systems sampled contained levels of atrazine below 0.1 ug/L (Boland, 1981). Drinking water in some areas may not contain any atrazine at all. Sufficient monitoring data are not available to determine regional variations in levels of exposure to atrazine from drinking water.

The daily intake of atrazine was estimated using the assumptions listed in Table IV-1 and the values presented above. The estimated daily intake of atrazine from drinking water ranges from 0.0 to 0.45 ug/kg/day, as shown in

Table A-1. Estimated Daily Intake of Atrazine From Drinking Water

Drinking water concentration[a] (ug/L)	Intake (ug/kg/day)
0.1	0.003
2.9	0.083
15.9	0.45

[a] Assumption: 70-kg adult male consumes 2 liters of water/day.

SOURCE: Adapted from Baker et al. (1981) and Boland (1981).

Table IV-1. The values presented do not account for variances in individual exposures or uncertainties in the assumptions used to estimate exposure levels.

2. Diet

Data obtained on levels of atrazine in foods in the United States were insufficient for use in determining typical dietary intake levels. Tolerances set by the U.S. Environmental Protection Agency (U.S. EPA, 1986b) for atrazine in and on raw agricultural commodities are presented in Table IV-2. It is not expected, however, that individuals would be exposed to all the foods listed in Table IV-2 at their tolerance levels.

3. Air

No data were obtained on levels of atrazine in ambient air. Therefore, the intake of atrazine from ambient air could not be estimated.

B. SUMMARY

Data on the intake of atrazine from drinking water, food, and ambient air are insufficient for use in determining which of the three sources is the major contributor to total intake.

Table A-2. Tolerances for Atrazine In and On Raw Agricultural Commodities

Commodity	Tolerance (ug/kg food)
Cattle	
fat	20 (N)[a]
meat by-products	20 (N)
meat	20 (N)
Corn fodder	
field	15,000
pop	15,000
sweet	15,000
Corn, forage	
field	15,000
pop	15,000
sweet	15,000
Corn	
fresh, including sweet[b]	250
grain	250
Eggs	20 (N)
Goats	
fat	20 (N)
meat by-products	20 (N)
meat	20 (N)
Grass	
range	4,000[c]
rye, perennial	15,000
Hogs	
fat	20 (N)
meat by-products	20 (N)
meat	20 (N)
Horses	
fat	20 (N)
meat by-products	20 (N)
meat	20 (N)

Table A-2. (continued)

Commodity	Tolerance (ug/kg food)
Macadamia nuts	250
Milk	20 (N)
Pineapples	250
fodder	10,000
forage	10,000
Poultry	
fat	20 (N)
meat by-products	20 (N)
meat	20 (N)
Proso millet	
fodder	5,000
forage	5,000
grain	250
straw	5,000
Sheep	
fat	20 (N)
meat by-products	20 (N)
meat	20 (N)
Sorghum	
fodder	15,000
forage	15,000
grain	250
Sugarcane	250
fodder	250
forage	250
Wheat	
fodder	5,000
grain	250
straw	5,000

a(N) = Negligible residue.
bKernel plus cob with husk removed.
cFor combined residues of atrazine and its metabolites.

SOURCE: Adapted from U.S. EPA (1986b).

C. REFERENCES

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